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Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders

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RESPIRATORY HEALTH EFFECTS OF PASSIVE SMOKING: LUNG CANCER AND OTHER DISORDERS

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PREFACE

This assessment of the respiratory health effects associated with passive smoking has been prepared by the Human Health Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, which is responsible for the report's scientific accuracy and conclusions. The assessment was prepared at the request of the Indoor Air Division, Office of Atmospheric and Indoor Air Programs, Office of Air and Radiation, which defined the assessment's scope and provided funding.

The report has been developed under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants.

Two drafts of this report were made available for public review and comments, the first in June 1990 (reviewed by the Agency's Science Advisory Board [SAB] in December 1990) and a significantly revised draft in May 1992 (reviewed by the SAB in July 1992). This report reflects the comments received from those reviews.

A comprehensive search of the scientific literature for this report is complete through September 1991. In addition, pertinent studies published through July 1992 have been included in the analysis in response to recommendations made by reviewers.

Due to both resource and time constraints, the scope of this report has been limited to an analysis of respiratory effects, primarily lung cancer in nonsmoking adults and noncancer respiratory illnesses in children, with emphasis on the epidemiologic data. Further, because two thorough reviews on passive smoking were completed in 1986 (by the U.S. Surgeon General and the National Research Council), this document provides a summary of those reports with a more comprehensive analysis of the literature appearing subsequent to those reports and an integration of the results.

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This document was prepared by the Office of Health and Environmental Assessment (OHEA) within the Office of Research and Development, with major contract funding provided by the Indoor Air Division within the Office of Air and Radiation's Office of Atmospheric and Indoor Air Programs. Steven P. Bayard[1] was the OHEA project manager with overall responsibility for the contents of this report and its conclusions. Other OHEA staff members responsible for the scientific content of sections of this document are Jennifer Jinot[1] and Aparna M. Koppikar.[1] Jennifer Jinot and Steven Bayard were the scientific editors.

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REVIEWERS

This final report was preceded by two earlier drafts: an External Review Draft (EPA/600/6-90/006A) published in May 1990, and an SAB Review Draft (EPA/600/6-90/006B) published in May 1992. The External Review Draft was released for public review and comment on June 25, 1990, and was subsequently reviewed by the EPA Science Advisory Board (SAB) on December 4 and 5, 1990. The SAB Review Draft incorporated many of the public comments and especially the valuable advice presented in the SAB's April 19, 1991, report to the Agency. In addition, many reviewers both within and outside the Agency provided assistance at various internal review stages.

The second Review Draft also was reviewed by the SAB on July 21 and 22, 1992, which provided its report to the Agency on November 20, 1992. The authors wish to thank all those who sought to improve the quality of this report with their comments and are particularly grateful to the SAB for its advice.

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- Staff from R.O.W. Sciences, Inc., under the direction of Kay Marshall, who were responsible for editing, word processing, and proofreading the final report.
- Robert Flaak, Assistant Staff Director of the SAB, whose efforts and professionalism in organizing and coordinating the two SAB reviews led to an improved and more useful product.

1. SUMMARY AND CONCLUSIONS

1.1. MAJOR CONCLUSIONS

Based on the weight of the available scientific evidence, the U.S. Environmental Protection Agency (EPA) has concluded that the widespread exposure to environmental tobacco smoke (ETS) in the United States presents a serious and substantial public health impact.

In adults:

- ETS is a human lung carcinogen, responsible for approximately 3,000 lung cancer deaths annually in U.S. nonsmokers.

In children:

- ETS exposure is causally associated with an increased risk of lower respiratory tract infections (LRIs) such as bronchitis and pneumonia. This report estimates that 150,000 to 300,000 cases annually in infants and young children up to 18 months of age are attributable to ETS.

- ETS exposure is causally associated with increased prevalence of fluid in the middle ear, symptoms of upper respiratory tract irritation, and a small but significant reduction in lung function.

- ETS exposure is causally associated with additional episodes and increased severity of symptoms in children with asthma. This report estimates that 200,000 to 1,000,000 asthmatic children have their condition worsened by exposure to ETS.

- ETS exposure is a risk factor for new cases of asthma in children who have not previously displayed symptoms.

1.2. BACKGROUND

Tobacco smoking has long been recognized (e.g., U.S. Department of Health, Education, and Welfare [U.S. DHEW], 1964) as a major cause of mortality and morbidity, responsible for an estimated 434,000 deaths per year in the United States (Centers for Disease Control [CDC], 1991a). Tobacco use is known to cause cancer at various sites, in particular the lung (U.S. Department of Health and Human Services [U.S. DHHS], 1982; International Agency for Research on Cancer [IARC], 1986). Smoking can also cause respiratory diseases (U.S. DHHS, 1984, 1989) and is a major risk factor for heart disease (U.S. DHHS, 1983). In recent years, there has been concern that nonsmokers may also be at risk for some of these health effects as a result of their exposure ("passive smoking") to the tobacco smoke that occurs in various environments occupied by smokers. Although this ETS is dilute compared with the mainstream smoke (MS) inhaled by active smokers, it is chemically similar, containing many of the same carcinogenic and toxic agents.

In 1986, the National Research Council (NRC) and the Surgeon General of the U.S. Public Health Service independently assessed the health effects of exposure to ETS (NRC, 1986; U.S. DHHS, 1986). Both of the 1986 reports conclude that ETS can cause lung cancer in adult nonsmokers and that children of parents who smoke have increased frequency of respiratory symptoms and acute lower respiratory tract infections, as well as evidence of reduced lung function.

More recent epidemiologic studies of the potential associations between ETS and lung cancer in nonsmoking adults and between ETS and noncancer respiratory effects more than double the size of the database available for analysis from that of the 1986 reports. This EPA report critically reviews the current database on the respiratory health effects of passive smoking; these data are utilized to develop a hazard identification for ETS and to make quantitative estimates of the public health impacts of ETS for lung cancer and various other respiratory diseases.

The weight-of-evidence analysis for the lung cancer hazard identification is developed in accordance with U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a) and established principles for evaluating epidemiologic studies. The analysis considers animal bioassays and genotoxicity studies, as well as biological measurements of human uptake of tobacco smoke components and epidemiologic data on active and passive smoking. The availability of abundant and consistent human data, especially human data at actual environmental levels of exposure to the specific agent (mixture) of concern, allows a hazard identification to be made with a high degree of certainty. The conclusive evidence of the dose-related lung carcinogenicity of

MS in active smokers (Chapter 4), coupled with information on the chemical similarities of MS and ETS and evidence of ETS uptake in nonsmokers (Chapter 3), is sufficient by itself to establish ETS as a known human lung carcinogen, or "Group A" carcinogen under U.S. EPA's carcinogen classification system. In addition, this document concludes that the overall results of 30 epidemiologic studies on lung cancer and passive smoking (Chapter 5), using spousal smoking as a surrogate of ETS exposure for female never-smokers, similarly justify a Group A classification.

The weight-of-evidence analyses for the noncancer respiratory effects are based primarily on a review of epidemiologic studies (Chapter 7). Most of the endpoints examined are respiratory disorders in children, where parental smoking is used as a surrogate of ETS exposure. For the noncancer respiratory effects in nonsmoking adults, most studies used spousal smoking as an exposure surrogate. A causal association was concluded to exist for a number of respiratory disorders where there was sufficient consistent evidence for a biologically plausible association with ETS that could not be explained by bias, confounding, or chance. The fact that the database consists of human evidence from actual environmental exposure levels gives a high degree of confidence in this conclusion. Where there was suggestive but inconclusive evidence of causality, as was the case for asthma induction in children, ETS was concluded to be a risk factor for that endpoint. Where data were inconsistent or inadequate for evaluation of an association, as for acute upper respiratory tract infections and acute middle ear infections in children, no conclusions were drawn.

This report also has attempted to provide estimates of the extent of the public health impact, where appropriate, in terms of numbers of ETS-attributable cases in nonsmoking subpopulations. Unlike for qualitative hazard identification assessments, where information from many sources adds to the confidence in a weight-of-evidence conclusion, for quantitative risk assessments, the usefulness of studies usually depends on how closely the study population resembles nonsmoking segments of the general population. For lung cancer estimates among U.S. nonsmokers, the substantial epidemiology database of ETS and lung cancer among U.S. female never-smokers was considered to provide the most appropriate information. From these U.S. epidemiology studies, a pooled relative risk estimate was calculated and used in the derivation of the population risk estimates. The large number of studies available, the generally consistent results, and the condition of actual environmental levels of exposure increase the confidence in these estimates. Even under these circumstances, however, uncertainties remain, such as in the use of questionnaires and current biomarker measurements to estimate past exposure, assumptions of exposure-response linearity, and extrapolation to male never-smokers and to ex-smokers. Still, given the strength of the evidence for the lung carcinogenicity of tobacco smoke and the extensive human database from actual environmental exposure levels, fewer assumptions are necessary than

is usual in EPA quantitative risk assessments, and confidence in these estimates is rated medium to high.

Population estimates of ETS health impacts are also made for certain noncancer respiratory endpoints in children, specifically lower respiratory tract infections (i.e., pneumonia, bronchitis, and bronchiolitis) and episodes and severity of attacks of asthma. Estimates of ETS-attributable cases of LRI in infants and young children are thought to have a high degree of confidence because of the consistent study findings and the appropriateness of parental smoking as a surrogate measure of exposure in very young children. Estimates of the number of asthmatic children whose condition is aggravated by exposure to ETS are less certain than those for LRIs because of different measures of outcome in various studies and because of increased extraparental exposure to ETS in older children. Estimates of the number of new cases of asthma in previously asymptomatic children also have less confidence because at this time the weight of evidence for asthma induction, while suggestive of a causal association, is not conclusive.

Most of the ETS population impact estimates are presented in terms of ranges, which are thought to reflect reasonable assumptions about the estimates of parameters and variables required for the extrapolation models. The validity of the ranges is also dependent on the appropriateness of the extrapolation models themselves.

While this report focuses only on the respiratory health effects of passive smoking, there also may be other health effects of concern. Recent analyses of more than a dozen epidemiology and toxicology studies (e.g., Steenland, 1992; National Institute for Occupational Safety and Health [NIOSH], 1991) suggest that ETS exposure may be a risk factor for cardiovascular disease. In addition, a few studies in the literature link ETS exposure to cancers of other sites; at this time, that database appears inadequate for any conclusion. This report does not develop an analysis of either the nonrespiratory cancer or the heart disease data and takes no position on whether ETS is a risk factor for these diseases. If it is, the total public health impact from ETS will be greater than that discussed here.

1.3. PRIMARY FINDINGS

A. Lung Cancer in Nonsmoking Adults

1. Passive smoking is causally associated with lung cancer in adults, and ETS, by the total weight of evidence, belongs in the category of compounds classified by EPA as Group A (known human) carcinogens.
2. Approximately 3,000 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are estimated to be attributable to ETS in the United States. While there are statistical and modeling uncertainties

in this estimate, and the true number may be higher or lower, the assumptions used in this analysis would tend to underestimate the actual population risk. The overall confidence in this estimate is medium to high.

B. Noncancer Respiratory Diseases and Disorders

1. Exposure of children to ETS from parental smoking is causally associated with:
   a. increased prevalence of respiratory symptoms of irritation (cough, sputum, and wheeze),
   b. increased prevalence of middle ear effusion (a sign of middle ear disease), and
   c. a small but statistically significant reduction in lung function as tested by objective measures of lung capacity.
2. ETS exposure of young children and particularly infants from parental (and especially mother's) smoking is causally associated with an increased risk of LRIs (pneumonia, bronchitis, and bronchiolitis). This report estimates that exposure to ETS contributes 150,000 to 300,000 LRIs annually in infants and children less than 18 months of age, resulting in 7,500 to 15,000 hospitalizations. The confidence in the estimates of LRIs is high. Increased risks for LRIs continue, but are lower in magnitude, for children until about age 3; however, no estimates are derived for children over 18 months.
3. a. Exposure to ETS is causally associated with additional episodes and increased severity of asthma in children who already have the disease. This report estimates that ETS exposure exacerbates symptoms in approximately 20% of this country's 2 million to 5 million asthmatic children and is a major aggravating factor in approximately 10%.
   b. In addition, the epidemiologic evidence is suggestive but not conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms. Based on this evidence and the known ETS effects on both the immune system and lungs (e.g., atopy and airway hyperresponsiveness), this report concludes that ETS is a risk factor for the induction of asthma in previously asymptomatic children. Data suggest that relatively high levels of exposure are required to induce new cases of asthma in children. This report calculates that previously asymptomatic children exposed to ETS from mothers who smoke at least 10 cigarettes per day will exhibit an estimated 8,000 to 26,000 new cases of

asthma annually. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

4. Passive smoking has subtle but significant effects on the respiratory health of nonsmoking adults, including coughing, phlegm production, chest discomfort, and reduced lung function.

This report also has reviewed data on the relationship of maternal smoking and sudden infant death syndrome (SIDS), which is thought to involve some unknown respiratory pathogenesis. The report concludes that while there is strong evidence that infants whose mothers smoke are at an increased risk of dying from SIDS, available studies do not allow us to differentiate whether and to what extent this increase is related to in utero versus postnatal exposure to tobacco smoke products. Consequently, this report is unable to assert whether or not ETS exposure by itself is a risk factor for SIDS independent of smoking during pregnancy.

Regarding an association of parental smoking with either upper respiratory tract infections (colds and sore throats) or acute middle ear infections in children, this report finds the evidence inconclusive.

1.3.1. ETS and Lung Cancer

1.3.1.1. *Hazard Identification*

The Surgeon General (U.S. DHHS, 1989) estimated that smoking was responsible for more than one of every six deaths in the United States and that it accounted for about 90% of the lung cancer deaths in males and about 80% in females in 1985. Smokers, however, are not the only ones exposed to tobacco smoke. The sidestream smoke (SS) emitted from a smoldering cigarette between puffs (the main component of ETS) has been documented to contain virtually all of the same carcinogenic compounds (known and suspected human and animal carcinogens) that have been identified in the mainstream smoke (MS) inhaled by smokers (Chapter 3). Exposure concentrations of these carcinogens to passive smokers are variable but much lower than for active smokers. An excess cancer risk from passive smoking, however, is biologically plausible.

Based on the firmly established causal association of lung cancer with active smoking with a dose-response relationship down to low doses (Chapter 4), passive smoking is considered likely to affect the lung similarly. The widespread presence of ETS in both home and workplace and its absorption by nonsmokers in the general population have been well documented by air sampling and by body measurement of biomarkers such as nicotine and cotinine (Chapter 3). This raises the question of whether any direct evidence exists for the relationship between ETS exposure and lung cancer in the general population and what its implications may be for public health. This

report addresses that question by reviewing and analyzing the evidence from 30 epidemiologic studies of effects from normally occurring environmental levels of ETS (Chapter 5). Because there is widespread exposure and it is difficult to construct a truly unexposed subgroup of the general population, these studies attempt to compare individuals with higher ETS exposure to those with lower exposures. Typically, female never-smokers who are married to a smoker are compared with female never-smokers who are married to a nonsmoker. Some studies also consider ETS exposure of other subjects (i.e., male never-smokers and long-term former smokers of either sex) and from other sources (e.g., workplace and home exposure during childhood), but these studies are fewer and represent fewer cases, and they are generally excluded from the analysis presented here. Use of the female never-smoker studies provides the largest, most homogeneous database for analysis to determine whether an ETS effect on lung cancer is present. This report assumes that the results for female never-smokers are generalizable to all nonsmokers.

Given that ETS exposures are at actual environmental levels and that the comparison groups are both exposed to appreciable background (i.e., nonspousal) ETS, any excess risk for lung cancer from exposure to spousal smoke would be expected to be small. Furthermore, the risk of lung cancer is relatively low in nonsmokers, and most studies have a small sample size, resulting in a very low statistical power (probability of detecting a real effect if it exists). Besides small sample size and low incremental exposures, other problems inherent in several of the studies may also limit their ability to detect a possible effect. Therefore, this report examines the data in several different ways. After downward adjustment of the relative risks for smoker misclassification bias, the studies are individually assessed for strength of association, both for the overall data and for the highest exposure group when exposure-level data are available, and for exposure-response trend. Then the study results are pooled by country using statistical techniques for combining data, including both positive and nonpositive results, to increase the ability to determine whether or not there is an association between ETS and lung cancer. Finally, in addition to the previous statistical analyses that weight the studies only by size, regardless of design and conduct, the studies are qualitatively evaluated for potential confounding, bias, and likely utility to provide information about any lung carcinogenicity of ETS. Based on these qualitative considerations, the studies are categorized into one of four tiers and then statistically analyzed successively by tier.

Results from all of the analyses described above strongly support a causal association between lung cancer ETS exposure. The overall proportion (9/30) of individual studies found to show an association between lung cancer and spousal ETS exposure at all levels combined is unlikely to occur by chance ($p < 10^{-4}$). When the analysis focuses on higher levels of spousal exposure, every one of the 17 studies with exposure-level data shows increased risk in the highest

exposure group; 9 of these are significant at the $p < 0.05$ level, despite most having low power, another result highly unlikely to occur by chance ($p < 10^{-7}$). Similarly, the proportion (10/14; $p < 10^{-9}$) showing a statistically significant exposure-response trend is highly supportive of a causal association.

Combined results by country showed statistically significant associations for Greece (2 studies), Hong Kong (4 studies), Japan (5 studies), and the United States (11 studies), and in that order of strength of relative risk. Pooled results of the four Western European studies (three countries) actually showed a slightly stronger association than that of the United States, but it was not statistically significant, probably due to the smaller sample size. The combined results of the Chinese studies do not show an association between ETS and lung cancer; however, two of the four Chinese studies were designed mainly to determine the lung cancer effects of high levels of other indoor air pollutants indigenous to those areas, which would obscure a smaller ETS effect. These two Chinese studies do, however, provide very strong evidence on the lung carcinogenicity of these other indoor air pollutants, which contain many of the same components as ETS. When results are combined only for the other two Chinese studies, they demonstrate a statistically significant association for ETS and lung cancer.

The heterogeneity of observed relative risk estimates among countries could result from several factors. For example, the observed differences may reflect true differences in lung cancer rates for never-smokers, in ETS exposure levels from nonspousal sources, or in related lifestyle characteristics in different countries. For the time period in which ETS exposure was of interest for these studies, spousal smoking is considered to be a better surrogate for ETS exposure in more "traditional" societies, such as Japan and Greece, than in the United States. In the United States, other sources of ETS exposure (e.g., work and public places) are generally higher, which obscures the effects of spousal smoking and may explain the lower relative risks observed in the United States. Nevertheless, despite observed differences between countries, all showed evidence of increased risk.

Based on these analyses and following the U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight of evidence, principally:

- Biological plausibility. ETS is taken up by the lungs, and components are distributed throughout the body. The presence of the same carcinogens in ETS and MS, along with the established causal relationship between lung cancer and active smoking with the dose-response relationships exhibited down to low doses, establishes the plausibility that ETS is also a lung carcinogen.

- Supporting evidence from animal bioassays and genotoxicity experiments. The carcinogenicity of tobacco smoke has been demonstrated in lifetime inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of SS condensates has been shown in intrapulmonary implantations and skin painting experiments. Positive results of genotoxicity testing for both MS and ETS provide corroborative evidence for their carcinogenic potential.
- Consistency of response. All 4 of the cohort studies and 20 of the 26 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as ever exposed to any level of spousal ETS. Furthermore, every one of the 17 studies with response categorized by exposure level demonstrated increased risk for the highest exposure group. When assessment was restricted to the 19 studies judged to be of higher utility based on study design, execution, and analysis (Appendix A), 17 observed higher risks, and 6 of these increases were statistically significant, despite most having low statistical power. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.
- Broad-based evidence. These 30 studies provide data from 8 different countries, employ a wide variety of study designs and protocols, and are conducted by many different research teams. Results from all countries, with the possible exception of two areas of China where high levels of other indoor air lung carcinogens were present, show small to modest increases in lung cancer associated with spousal ETS exposure. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.
- Upward trend in exposure-response. Both the largest of the cohort studies--the Japanese study of Hirayama with 200 lung cancer cases--and the largest of the case-control studies--the U.S. study by Fontham and associates (1991) with 420 lung cancer cases and two sets of controls--demonstrate a strong exposure-related statistical association between passive smoking and lung cancer. This upward trend is well supported by the preponderance of epidemiology studies. Of the 14 studies that provide sufficient data for a trend test by exposure level, 10 were statistically significant despite most having low statistical power.
- Detectable association at environmental exposure levels. Within the population of married women who are lifelong nonsmokers, the excess lung cancer risk from

exposure to their smoking husbands' ETS is large enough to be observed, even for all levels of their spousal exposure combined. Carcinogenic responses are usually detectable only in high-exposure circumstances, such as occupational settings, or in experimental animals receiving very high doses. In addition, effects are harder to observe when there is substantial background exposure in the comparison groups, as is the case here.

- Effects remain after adjustment for potential upward bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk for ETS exposure. The evidence remains statistically significant and conclusive, however, after adjustments for smoker misclassification. For the United States, the summary estimate of relative risk from nine case-control plus two cohort studies is 1.19 (90% confidence interval [C.I.] = 1.04, 1.35; $p < 0.05$) after adjustment for smoker misclassification. For Greece, 2.00 (1.42, 2.83), Hong Kong, 1.61 (1.25, 2.06), and Japan, 1.44 (1.13, 1.85), the estimated relative risks are higher than those of the United States and more highly significant after adjusting for the potential bias.
- Strong associations for highest exposure groups. Examining the groups with the highest exposure levels increases the ability to detect an effect, if it exists. Nine of the sixteen studies worldwide for which there are sufficient exposure-level data are statistically significant for the highest exposure group, despite most having low statistical power. The overall pooled estimate of 1.81 for the highest exposure groups is highly statistically significant (90% C.I. = 1.60, 2.05; $p < 10^{-6}$). For the United States, the overall pooled estimate of 1.38 (seven studies, corrected for smoker misclassification bias) is also highly statistically significant (90% C.I. = 1.13, 1.70; $p = 0.005$).
- Confounding cannot explain the association. The broad-based evidence for an association found by independent investigators across several countries, as well as the positive exposure-response trends observed in most of the studies that analyzed for them, make any single confounder highly unlikely as an explanation for the results. In addition, this report examined potential confounding factors (history of lung disease, home heat sources, diet, occupation) and concluded that none of these factors could account for the observed association between lung cancer and ETS.

1.3.1.2. *Estimation of Population Risk*

The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard to the U.S. population because of the large number of smokers and the widespread presence of ETS. Current smokers comprise approximately 26% of the U.S. adult population and consume more than one-half trillion cigarettes annually (1.5 packs per day, on average), causing nearly universal exposure to at least some ETS. As a biomarker of tobacco smoke uptake, cotinine, a metabolite of the tobacco-specific compound nicotine, is detectable in the blood, saliva, and urine of persons recently exposed to tobacco smoke. Cotinine has typically been detected in 50% to 75% of reported nonsmokers tested (50% equates to 63 million U.S. nonsmokers age 18 or older).

The best estimate of approximately 3,000 lung cancer deaths per year in U.S. nonsmokers age 35 and over attributable to ETS (Chapter 6) is based on data pooled from all 11 U.S. epidemiologic studies of never-smoking women married to smoking spouses. Use of U.S. studies should increase the confidence in these estimates. Some mathematical modeling is required to adjust for expected bias from misclassification of smoking status and to account for ETS exposure from sources other than spousal smoking. The overall relative risk estimate of 1.19 for the United States, already adjusted for smoker misclassification bias, becomes 1.59 after adjusting for background ETS sources (1.34 for nonspousal exposures only). Assumptions are also needed to relate responses in female never-smokers to those in male never-smokers and ex-smokers of both sexes, and to estimate the proportion of the nonsmoking population exposed to various levels of ETS. Overall, however, the assumptions necessary for estimating risk add far less uncertainty than other EPA quantitative assessments. This is because the extrapolation for ETS is based on a large database of human studies, all at levels actually expected to be encountered by much of the U.S. population.

The components of the 3,000 lung cancer deaths figure include approximately 1,500 female never-smokers, 500 male never-smokers, and 1,000 former smokers of both sexes. More females are estimated to be affected because there are more female than male nonsmokers. These component estimates have varying degrees of confidence; the estimate of 1,500 deaths for female never-smokers has the highest confidence because of the extensive database. The estimate of 500 for male never-smokers is less certain because it is based on the female never-smoker response and is thought to be low because males are generally subject to higher background ETS exposures than females. Adjustment for this higher background exposure would lead to higher risk estimates. The estimate of 1,000 lung cancer deaths for former smokers of both sexes is

considered to have the lowest confidence, and the assumptions used are thought to make this estimate low as well.

Workplace ETS levels are generally comparable with home ETS levels, and studies using body cotinine measures as biomarkers demonstrate that nonspousal exposures to ETS are often greater than exposure from spousal smoking. Thus, this report presents an alternative breakdown of the estimated 3,000 ETS-attributable lung cancer deaths between spousal and nonspousal exposures. By extension of the results from spousal smoking studies, coupled with biological measurements of exposure, more lung cancer deaths are estimated to be attributable to ETS from combined nonspousal exposures--2,200 of both sexes--than from spousal exposure--800 of both sexes. This spouse-versus-other-sources partitioning depends on current exposure estimates that may or may not be applicable to the exposure period of interest. Thus, this breakdown contains this element of uncertainty in addition to those discussed above with respect to the previous breakdown.

An alternative analysis, based on the large Fontham et al. (1991) study, which is the only study that provides biomarker estimates of both relative risk and ETS exposure, yields population risk point estimates of 2,700 and 3,600. These population risk estimates are highly consistent with the estimate of 3,000 based on the combined U.S. studies.

While there is statistical variance around all of the parameters used in the quantitative assessment, the two largest areas of uncertainty are probably associated with the relative risk estimate for spousal ETS exposure and the parameter estimate for the background ETS exposure adjustment. A sensitivity analysis that independently varies these two estimates yields population risk estimates as low as 400 and as high as 7,000. These extremes, however, are considered unlikely; the more probable range is narrower, and the generally conservative assumptions employed suggest that the actual population risk number may be greater than 3,000. Overall, considering the multitude, consistency, and quality of all these studies, the weight-of-evidence conclusion that ETS is a known human lung carcinogen, and the limited amount of extrapolation necessary, the confidence in the estimate of approximately 3,000 lung cancer deaths is medium to high.

1.3.2. ETS and Noncancer Respiratory Disorders

Exposure to ETS from parental smoking has been previously linked with increased respiratory disorders in children, particularly in infants. Several studies have confirmed the exposure and uptake of ETS in children by assaying saliva, serum, or urine for cotinine. These cotinine concentrations were highly correlated with smoking (especially by the mother) in the child's presence. Nine to twelve million American children under 5 years of age, or one-half to

two-thirds of all children in this age group, may be exposed to cigarette smoke in the home (American Academy of Pediatrics, 1986; Overpeck and Moss, 1991).

With regard to the noncancer respiratory effects of passive smoking, this report focuses on epidemiologic evidence appearing since the two major reports of 1986 (NRC and U.S. DHHS) that bears on the potential association of parental smoking with detrimental respiratory effects in their children. These effects include symptoms of respiratory irritation (cough, sputum production, or wheeze); acute diseases of the lower respiratory tract (pneumonia, bronchitis, and bronchiolitis); acute middle ear infections and indications of chronic middle ear infections (predominantly middle ear effusion); reduced lung function (from forced expiratory volume and flow-rate measurements); incidence and prevalence of asthma and exacerbation of symptoms in asthmatics; and acute upper respiratory tract infections (colds and sore throats). The more than 50 recently published studies reviewed here essentially corroborate the previous conclusions of the 1986 reports of the NRC and Surgeon General regarding respiratory symptoms, respiratory illnesses, and pulmonary function, and they strengthen support for those conclusions by the additional weight of evidence (Chapter 7). For example, new data on middle ear effusion strengthen previous evidence to warrant the stronger conclusion in this report of a causal association with parental smoking. Furthermore, recent studies establish associations between parental smoking and increased incidence of childhood asthma. Additional research also supports the hypotheses that in utero exposure to mother's smoke and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization, changes that are known to predispose children to early respiratory illness. Early respiratory illness can lead to long-term pulmonary effects (reduced lung function and increased risk of chronic obstructive lung disease).

This report also summarizes the evidence for an association between parental smoking and SIDS, which was not addressed in the 1986 reports of the NRC or Surgeon General. SIDS is the most common cause of death in infants ages 1 month to 1 year. The cause (or causes) of SIDS is unknown; however, it is widely believed that some form of respiratory pathogenesis is generally involved. The current evidence strongly suggests that infants whose mothers smoke are at an increased risk of dying of SIDS, independent of other known risk factors for SIDS, including low birthweight and low gestational age, which are specifically associated with active smoking during pregnancy. However, available studies do not allow this report to conclude whether that increased risk is related to in utero versus postnatal exposure to tobacco smoke products, or to both.

The 1986 reports of the NRC and Surgeon General conclude that both the prevalence of respiratory symptoms of irritation and the incidence of lower respiratory tract infections are higher in children of smoking parents. In the 18 studies of respiratory symptoms subsequent to

the 2 reports, increased symptoms (cough, phlegm production, and wheezing) were observed in a range of ages from birth to midteens, particularly in infants and preschool children. In addition to the studies on symptoms of respiratory irritation, 10 new studies have addressed the topic of parental smoking and acute lower respiratory tract illness in children, and 9 have reported statistically significant associations. The cumulative evidence is conclusive that parental smoking, especially the mother's, causes an increased incidence of respiratory illnesses from birth up to the first 18 months to 3 years of life, particularly for bronchitis, bronchiolitis, and pneumonia. Overall, the evidence confirms and strengthens the previous conclusions of the NRC and Surgeon General.

Recent studies also solidify the evidence for the conclusion of a causal association between parental smoking and increased middle ear effusion in young children. Middle ear effusion is the most common reason for hospitalization of young children for an operation.

At the time of the Surgeon General's report on passive smoking (U.S. DHHS, 1986), data were sufficient to conclude only that maternal smoking may influence the severity of asthma in children. The recent studies reviewed here strengthen and confirm these exacerbation effects. The new evidence is also conclusive that ETS exposure increases the number of episodes of asthma in children who already have the disease. In addition, the evidence is suggestive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms, although the results are statistically significant only with children whose mothers smoke 10 or more cigarettes per day. While the evidence for new cases of asthma itself is not conclusive of a causal association, the consistently strong association of ETS both with increased frequency and severity of the asthmatic symptoms and with the established ETS effects on the immune system and airway hyperresponsiveness lead to the conclusion that ETS is a risk factor for induction of asthma in previously asymptomatic children.

Regarding the effects of passive smoking on lung function in children, the 1986 NRC and Surgeon General reports both conclude that children of parents who smoke have small decreases in tests of pulmonary output function of both the larger and smaller air passages when compared with the children of nonsmokers. As noted in the NRC report, if ETS exposure is the cause of the observed decrease in lung function, the effect could be due to the direct action of agents in ETS or an indirect consequence of increased occurrence of acute respiratory illness related to ETS.

Results from eight studies on ETS and lung function in children that have appeared since those reports add some additional confirmatory evidence suggesting a causal rather than an indirect relationship. For the population as a whole, the reductions are small relative to the interindividual variability of each lung function parameter. However, groups of particularly susceptible or heavily exposed children have shown larger decrements. The studies reviewed

suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. Exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

With respect to lung function effects in adults exposed to ETS, the 1986 NRC and Surgeon General reports found the data at that time inconclusive, due to high interindividual variability and the existence of a large number of other risk factors, but compatible with subtle deficits in lung function. Recent studies confirm the association of passive smoking with small reductions in lung function. Furthermore, new evidence also has emerged suggesting a subtle association between exposure to ETS and increased respiratory symptoms in adults.

Some evidence suggests that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

In reviewing the available evidence indicating an association (or lack thereof) between ETS exposure and the different noncancer respiratory disorders analyzed in this report, the possible role of several potential confounding factors was considered. These include other indoor air pollutants; socioeconomic status; effect of parental symptoms; and characteristics of the exposed child, such as low birthweight or active smoking. No single or combined confounding factors can explain the observed respiratory effects of passive smoking in children.

For diseases for which ETS has been either causally associated (LRIs) or indicated as a risk factor (asthma cases in previously asymptomatic children), estimates of population-attributable risk can be calculated. A population risk assessment (Chapter 8) provides a probable range of estimates that 8,000 to 26,000 cases of childhood asthma per year are attributable to ETS exposure from mothers who smoke 10 or more cigarettes per day. The confidence in this range of estimates is medium and is dependent on the suggestive evidence of the database. While the data show an effect only for children of these heavily smoking mothers, additional cases due to lesser ETS exposure also are a possibility. If the effect of this lesser exposure is considered, the range of estimates of new cases presented above increases to 13,000 to 60,000. Furthermore, this report estimates that the additional public health impact of ETS on asthmatic children includes more than 200,000 children whose symptoms are significantly aggravated and as many as 1,000,000 children who are affected to some degree.

This report estimates that ETS exposure contributes 150,000 to 300,000 cases annually of lower respiratory tract illness in infants and children younger than 18 months of age and that 7,500 to 15,000 of these will require hospitalization. The strong evidence linking ETS exposure to increased incidence of bronchitis, bronchiolitis, and pneumonia in young children gives these estimates a high degree of confidence. There is also evidence suggesting a smaller ETS effect on children between the ages of 18 months and 3 years, but no additional estimates have been computed for this age group. Whether or not these illnesses result in death has not been addressed here.

In the United States, more than 5,000 infants die of SIDS annually. It is the major cause of death in infants between the ages of 1 month and 1 year, and the linkage with maternal smoking is well established. The Surgeon General and the World Health Organization estimate that more than 700 U.S. infant deaths per year from SIDS are attributable to maternal smoking (CDC, 1991a, 1992b). However, this report concludes that at present there is not enough direct evidence supporting the contribution of ETS exposure to declare it a risk factor or to estimate its population impact on SIDS.

2. INTRODUCTION

An estimated 434,000 deaths per year in the United States, or more than one of every six deaths, are attributable to tobacco use, in particular cigarette smoking (CDC, 1991a; figures for 1988). Approximately 112,000 of these smoking-related deaths are from lung cancer, accounting for an estimated 87% of U.S. lung cancer mortality (U.S. DHHS, 1989). Cigarette smoking is also causally related to cancer at various other sites, such as the bladder, renal pelvis, pancreas, and upper respiratory and digestive tracts (IARC, 1986). Roughly 30,000 deaths per year from cancers at these sites are attributable to smoking (CDC, 1991a). Furthermore, smoking is the major cause of chronic obstructive pulmonary disease (COPD), which includes emphysema, and is thought to be responsible for approximately 61,000 COPD deaths yearly, or about 82% of COPD deaths (U.S. DHHS, 1989). Tobacco use is also a major risk factor for cardiovascular diseases, the leading cause of death in the United States. It is estimated that each year 156,000 heart disease deaths and 26,000 deaths from stroke are attributable to smoking (CDC, 1991a). In addition to this substantial mortality, the association of smoking with these conditions also involves significant morbidity.

Smoking also is a risk factor for various respiratory infections, such as influenza, bronchitis, and pneumonia. An estimated 20,000 influenza and pneumonia deaths per year are attributable to smoking (CDC, 1991a). Smokers also suffer from lung function impairment and numerous other respiratory symptoms, such as cough, phlegm production, wheezing, and shortness of breath. In addition, smokers are at increased risk for a variety of other conditions, including pregnancy complications and ulcers.

Although the exact mechanisms and tobacco smoke components associated with these health effects are not known with certainty, more than 40 known or suspected human carcinogens have been identified in tobacco smoke. These include, for example, benzene, nickel, polonium-210, 2-napthylamine, 4-aminobiphenyl, formaldehyde, various *N*-nitrosamines, benz[a]anthracene, and benzo[a]pyrene. Many other toxic agents, such as carbon monoxide, nitrogen oxides, ammonia, and hydrogen cyanide, are also found in tobacco smoke.

Smokers, however, are not the only ones at risk from exposure to these tobacco smoke toxicants. In utero exposure from maternal smoking during pregnancy is known to be associated with low birthweight and increased risk of fetal and infant death (U.S. DHHS, 1989). Furthermore, nonsmokers might be at risk for smoking-associated health effects from "passive smoking," or exposure to environmental tobacco smoke (ETS).

When a cigarette is smoked, approximately one-half of the smoke generated is sidestream smoke (SS) emitted from the smoldering cigarette between puffs. This SS contains essentially all of the same carcinogenic and toxic agents that have been identified in the mainstream smoke (MS) inhaled by the smoker (see Chapter 3). SS and exhaled MS are the major components of ETS. Environmental monitoring and measurements of biomarkers for ETS in the biological fluids of nonsmokers demonstrate that ETS constituents can be found at elevated levels in indoor environments where smoking occurs and that these constituents are inhaled and absorbed by nonsmokers (see Chapter 3).

Twenty-six percent of the U.S. adult population (CDC, 1992b), or about 50 million Americans, are smokers, and so virtually all Americans are likely to be exposed to some amount of ETS in the home, at work, or in public places. Measurements of biomarkers for ETS in nonsmokers confirm that nearly all Americans are exposed to ETS (see Chapter 3).

In view of the high levels of mortality and morbidity associated with smoking, the chemical similarity between ETS and MS, and the considerable likelihood for exposure of nonsmokers to ETS, passive smoking is potentially a substantial public health concern. The objectives of this report are to assess the risk to nonsmokers for respiratory health effects from exposure to ETS (hazard identification) and to estimate the population impact (quantitative population risk assessment) of any such ETS-attributable respiratory effects.

2.1. FINDINGS OF PREVIOUS REVIEWS

The first epidemiologic results associating passive smoking with lung cancer appeared in the early 1980's. Since then, two major comprehensive reviews of the health effects of passive smoking and several less extensive ones have been published. One of the major reviews was conducted by the National Research Council (NRC) in 1986. At the request of two Federal agencies, the U.S. Environmental Protection Agency and the U.S. Department of Health and Human Services, the NRC formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on all of the potential health consequences of exposure. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail and includes summary analyses from 10 case-control studies and 3 cohort (prospective) studies. The report concludes that "considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers." Combining the data from all the studies, the committee calculated an overall observed relative risk estimate of 1.34 (95% C.I. = 1.18, 1.53).

The NRC committee was concerned about potential bias in the study results caused by current and former smokers incorrectly self-reported as lifelong nonsmokers (never-smokers). Using plausible assumptions for misreported smoking habits, the committee determined that smoker misclassification cannot account for all of the increased risk observed in the epidemiologic studies. Furthermore, the upward bias on the relative risk of lung cancer caused by smoker misclassification is counterbalanced by the downward bias from background ETS exposure to the supposedly unexposed group. Correcting for smoker misclassification and background ETS exposure, the committee calculated an overall adjusted relative risk estimate of 1.42 (range of 1.24 to 1.61) for lung cancer in nonsmokers from exposure to ETS from spousal smoking plus background sources.

The NRC committee also found evidence for noncancer respiratory effects in children exposed to ETS. It recommended that "in view of the weight of the scientific evidence that ETS exposure in children increases the frequency of pulmonary symptoms and respiratory infections, it is prudent to eliminate smoking and resultant ETS from the environments of small children." Furthermore, the committee concluded that "household exposure to ETS is linked with increased rates of chronic ear infections and middle ear effusions in young children." The NRC report also notes that "evidence has accumulated indicating that nonsmoking pregnant women exposed to ETS on a daily basis for several hours are at increased risk for producing low-birthweight babies, through mechanisms which are, as yet, unknown."

The second major review, the Surgeon General's report on the health consequences of passive smoking, also appeared in 1986 (U.S. DHHS, 1986). This review covers ETS chemistry, exposure, and various health effects, primarily lung cancer and childhood respiratory diseases. On the subject of lung cancer, the report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer.

With respect to respiratory disorders in children, the Surgeon General's report determined that "the children of parents who smoke, compared with the children of nonsmoking parents, have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increase in lung function as the lung matures."

In 1987, a committee of the International Agency for Research on Cancer (IARC) issued a report on methods of analysis and exposure measurement related to passive smoking (IARC,

1987a). The committee reviewed the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. The report borrows the summary statement on passive smoking from a previous IARC document that dealt mainly with tobacco smoking (IARC, 1986). The working group that produced the 1986 report had found that the epidemiologic evidence then available on passive smoking was compatible with either the presence or the absence of a lung cancer risk; however, based on other considerations related to biological plausibility, it concluded that passive smoking gives rise to some risk of cancer. Specifically, the 1986 IARC report states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive smoking," and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens . . . leads to the conclusion that passive smoking gives rise to some risk of lung cancer.

More recently, the Working Group on Passive Smoking, an independent international panel of scientists supported in part by RJR Reynolds Nabisco, reported the findings of its comprehensive "best-evidence synthesis" of over 2,900 articles on the health effects of passive smoking (Spitzer et al., 1990). The group concluded that "the weight of evidence is compatible with a positive association between residential exposure to environmental tobacco smoke (primarily from spousal smoking) and the risk of lung cancer." It also found "strong evidence that children exposed in the home to environmental tobacco smoke have higher rates of hospitalization (50% to 100%) for severe respiratory illness" and that the "evidence strongly supports a relationship between exposure to environmental tobacco smoke and asthma among children." In addition, the working group reported that there is evidence for associations between home ETS exposure and many chronic and acute respiratory illnesses, as well as small decreases in physiologic measures of respiratory function, in both children and adults. Evidence demonstrating an increased prevalence of otitis media (inflammation of the middle ear) in children exposed to ETS at home was also noted. With respect to in utero exposure, the group concluded that active maternal smoking is associated with reduced birthweight and with increased infant mortality.

A recent review of the health effects associated with adult workplace exposure to ETS conducted by the National Institute for Occupational Safety and Health (NIOSH, 1991) determined that "the collective weight of evidence (i.e., that from the Surgeon General's reports, the similarities in composition of MS and ETS, and the recent epidemiologic studies) is sufficient to conclude that ETS poses an increased risk of lung cancer and possibly heart disease to occupationally exposed workers." Furthermore:

Although these data were not gathered in an occupational setting, ETS meets the criteria of the Occupational Safety and Health Administration (OSHA) for classification as a potential occupational carcinogen [Title 29 of the Code of Federal Regulations, Part 1990]. NIOSH therefore recommends that exposures be reduced to the lowest feasible concentration.

The classification of "potential occupational carcinogen" is NIOSH's category of strongest evidence for carcinogenicity.

2.2. DEVELOPMENT OF EPA REPORT

2.2.1. Scope

Due to the serious health concerns that have arisen regarding ETS, a virtually ubiquitous indoor air pollutant, and the wealth of new information that has become available since the extensive 1986 reviews, the EPA has performed its own analytical hazard identification and population risk assessment for the respiratory health effects of passive smoking, based on a critical review of the data currently available, with an emphasis on the abundant epidemiologic evidence. The number of lung cancer studies analyzed in this document is more than double the number reviewed in 1986 (31 vs. 13), with a total of about 3,000 lung cancer cases in female nonsmokers now reported in case-control studies and almost 300,000 female nonsmokers followed by cohort studies. Furthermore, the database on passive smoking and respiratory disorders in children contains more than 50 new studies, including 9 additional studies on acute lower respiratory tract illnesses, 10 on acute and chronic middle ear diseases, 18 on respiratory symptoms, 10 on asthma, and 8 on lung function. This report also discusses six recent studies of the effects of passive smoking on adult respiratory symptoms and lung function. Finally, eight studies of maternal smoking and sudden infant death syndrome (SIDS), which was not addressed in the NRC report or the Surgeon General's report, are reviewed. (Although the cause of SIDS is unknown, the most widely accepted hypotheses suggest that some form of respiratory pathogenesis is usually involved.)

First, this report reviews information on the nature of ETS and human exposures. Then, in accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), it critically analyzes human, animal, and genotoxicity data to establish the weight of evidence for the hazard identification of ETS as a human lung carcinogen and to characterize the U.S. population risk. Similarly, it reviews studies of passive smoking and noncancer respiratory disorders, particularly in children, and provides both hazard identification and population risk estimates for some of these effects.

While this report restricts analysis to ETS-associated respiratory effects because of time and resource considerations, several recent studies have also linked passive smoking with an increased risk of heart disease or cancers at sites other than the lung. For cancers of other sites, the available evidence is quite limited (e.g., Hirayama, 1984; Sandler et al., 1985), but three recent analyses, examining over 15 epidemiologic studies and various supporting mechanistic studies, suggest that ETS is an important risk factor for heart disease, accounting for as many as 35,000 to 40,000 deaths annually (Wells, 1988; Glantz and Parmley, 1991; Steenland, 1992). This report takes no position on ETS and heart disease.

Other health effects of active smoking may also have passive smoking correlates of public health concern. Maternal smoking during pregnancy, for example, is known to affect fetal development. Studies on passive smoking during pregnancy are far fewer but have demonstrated an apparent association with low birthweight (e.g., Martin and Bracken, 1986). Furthermore, passive exposure to tobacco smoke products both in utero (during pregnancy) and postnatally (after birth) may result in other nonrespiratory developmental effects in children--for example, decrements in neurological development (Makin et al., 1991). Again, this report takes no position on these potential nonrespiratory effects.

2.2.2. Use of EPA's Guidelines

The lung cancer hazard identification and risk characterization for ETS are conducted in accordance with the EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a). In fact, tobacco smoke is a mixture of more than 4,000 compounds and could be evaluated according to the *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b). Such a highly complex mixture, however, is not easily characterized with respect to chemical composition, levels of exposure, and toxicity of constituents. Furthermore, the effects and mechanisms of interactions among chemicals are insufficiently understood.

The *Guidelines for the Health Risk Assessment of Chemical Mixtures* acknowledges these inherent uncertainties and recommends various assessment approaches, depending on the nature and quality of the data. When adequate data are available on health effects and exposure for the actual mixture of concern, as is the case with both MS and ETS, the preferred approach, according to the mixtures guidelines, is to adopt the procedures used for single compounds described by the *Guidelines for Carcinogen Risk Assessment*, as is done here. The EPA also has used this strategy for assessments of diesel exhausts, PCBs, and unleaded gasoline. The compilation of health effects and exposure information for all the mixture components of interest is considered optional. In the case of tobacco smoke, compiling this information would be highly

impractical due to the large number of components and the highly complex and changing nature of this mixture. It is also considered unnecessary, given the abundant epidemiologic data on ETS and lung cancer.

The *Guidelines for Carcinogen Risk Assessment* provide a general framework for the analysis of carcinogenic risk, while permitting "sufficient flexibility to accommodate new knowledge and new assessment methods as they emerge" (U.S. EPA, 1986a). According to the guidelines, a qualitative risk assessment, or hazard identification, is performed by evaluating all of the relevant data to determine if a compound has carcinogenic potential. Then, a dose-response assessment is made by using mathematical models to extrapolate from high experimental or occupational exposures, where risks are usually detected, to lower environmental exposure levels. Finally, the dose-response assessment and an exposure assessment are integrated into a risk characterization, providing risk estimates for exposed populations. The risk characterization also describes the assumptions and uncertainties in the estimate.

The enormous databases on active and passive smoking provide more than sufficient human evidence on which to base a hazard identification of ETS. The use of human evidence eliminates the uncertainties that normally arise when one has to base hazard identification on the results of high-dose animal experiments. Furthermore, the epidemiologic data on passive smoking provide direct evidence from environmental exposure levels, obviating the need for a dose-response extrapolation from high to low doses. These low-level environmental exposures, however, are associated with low relative risks that can only be detected in well-designed studies of sufficiently large size. For this reason, new assessment methods are used to categorize studies on the basis of quality criteria and to combine studies to increase the statistical power. Combining studies also provides a means for incorporating both positive and nonpositive study results into the statistical analysis.

As an alternative to using actual epidemiologic data on ETS, an ETS risk assessment could have used "cigarette-equivalents" to correlate ETS exposure with lung cancer risk based on dose-response models from active smoking. This would have involved using measures such as cotinine or respirable suspended particles to compare smoke uptake between smokers and ETS-exposed nonsmokers in order to equate passive smoking to the active smoking of some quantity of a cigarette(s). Then the carcinogenic response associated with that exposure level would be estimated from extrapolation models based on the dose-response relationships observed for active smoking. This procedure was not used for several reasons. Although MS and ETS are qualitatively similar with respect to chemical composition (i.e., they contain most, if not all, of the same toxicants and carcinogens), the absolute and proportional quantities of the components, as

well as their physical state, can differ substantially. Many tobacco smoke compounds partition preferentially into the MS component of smoke emissions; others, however, such as certain highly carcinogenic *N*-nitrosamines, are preferentially produced at lower temperatures and appear in much greater amounts in the ETS fraction. In addition, active and passive smokers have different breathing patterns, and particles in ETS are smaller than those in MS. Therefore, the distribution and deposition of smoke constituents in the respiratory tracts of active and passive smokers will not be identical. Furthermore, it is not known which of the chemicals in tobacco smoke are responsible for its carcinogenicity. Clearly, the comparison of a small number of biomarker measures cannot adequately quantify differential distributions of unknown carcinogenic compounds.

Another area of uncertainty in the "cigarette-equivalents" approach relates to potential metabolic differences between active and passive smokers. Active smoking is known to induce chemical- and drug-metabolizing enzymes in various tissues to levels that significantly exceed those found in nonsmokers. Thus, the dose-response relationships for tobacco smoke-associated health effects are likely to be nonlinear. In fact, evidence suggests that a linear dose-response extrapolation might underestimate the risk of adverse health effects from low doses of tobacco smoke (Remmer, 1987). Because of these uncertainties, the data from active smoking are more appropriate for qualitative hazard identification than for quantitative dose-response assessment. Furthermore, at least for lung cancer and other respiratory effects, we have substantial epidemiologic data from actual exposure of nonsmokers to environmental levels of genuine ETS, which constitute a superior database from which to derive quantitative risk estimates for passive smoking, without the need for low-dose extrapolation.

2.2.3. Contents of This Report

ETS is chemically similar to MS, containing most, if not all, of the same toxicants and known or suspected human carcinogens. A major difference, however, is that ETS is rapidly diluted into the environment, and consequently, passive smokers are exposed to much lower concentrations of these agents than are active smokers. Therefore, in assessing potential health risks attributable to ETS, it is important to be able to measure ETS levels in the many environments where it is found and to quantify actual human ETS exposure. The physical and chemical nature of ETS and issues related to human exposure are discussed in Chapter 3. The use of marker compounds and various methods for assessing ambient ETS concentrations, as well as the use of biomarkers and questionnaires to determine human exposure, is described. Furthermore, measurements of ETS components in various indoor environments and of ETS

constituents and their metabolites in nonsmokers are presented, providing evidence of actual nonsmoker exposure and uptake.

Chapter 4 reviews the major evidence that conclusively establishes that the tobacco smoke inhaled from active smoking is a human lung carcinogen. Unequivocal dose-response relationships exist between tobacco smoking and lung cancer, with no evidence of a threshold level of exposure. Supporting evidence for the carcinogenicity of tobacco smoke from animal bioassays and genotoxicity experiments is also summarized, including data from the limited animal and mutagenicity studies pertaining specifically to ETS or SS.

The chemical similarity between MS and ETS and the measurable uptake of ETS constituents by nonsmokers (Chapter 3), as well as the causal dose-related association between tobacco smoking and lung cancer in humans, extending to the lowest observed doses, and the corroborative evidence for the carcinogenicity of both MS and ETS provided by animal bioassays and genotoxicity studies (Chapter 4), clearly establish the biological plausibility that ETS is also a human lung carcinogen. In fact, this evidence is sufficient in its own right to establish the weight of evidence for ETS as a Group A (known human) carcinogen under EPA guidelines.

In addition to the evidence of human carcinogenicity from high exposures to tobacco smoke from active smoking, there are now more than 30 epidemiologic studies investigating lung cancer in nonsmokers exposed to actual ambient levels of ETS. The majority of these studies examine never-smoking women, with spousal smoking used as a surrogate for ETS exposure. Female exposure from spousal smoking is considered to be the single surrogate measure that is the most stable and best represents ETS exposure. Spousal smoking is, however, a crude surrogate, subject to exposure misclassification in both directions, since it actually constitutes only a varying portion of total exposure.

For the purposes of the hazard identification analysis in Chapter 5, which is based primarily on the epidemiologic studies of ETS, this document extensively and critically evaluates 31 epidemiologic studies from 8 different countries, including 11 studies from the United States (Appendix A). More than half of these studies have appeared since the NRC and Surgeon General's reviews were issued in 1986. Two U.S. studies are of particular interest. The recently published five-center study of Fontham et al. (1991) is a well-designed and well-conducted case-control study with 429 never-smoking female lung cancer cases and two separate sets of controls. This is the largest case-control study to date, and it has a high statistical power to detect the small increases in lung cancer risk that might be expected from ambient exposures. Furthermore, the Fontham et al. study is the only lung cancer study that also measured urinary cotinine levels as a biomarker of exposure. Another large U.S. case-control study was the recent

study by Janerich et al. (1990), with 191 cases. Both of these studies were supported by the National Cancer Institute.

In evaluating epidemiologic studies, potential sources of bias and confounding also must be addressed. Smoker misclassification of current and former smokers as never-smokers is the one identified source of systematic upward bias to the relative risk estimates. Therefore, prior to the analyses of the epidemiologic data that are conducted in Chapters 5 and 6, the relative risk estimates from each study are adjusted for smoker misclassification using the methodology described in Appendix B. Other potential sources of bias and confounding are discussed in Chapter 5.

Chapter 5 quantitatively and qualitatively analyzes the epidemiologic data to determine the weight of evidence for the hazard identification of ETS. First, the individual studies are statistically assessed using tests for effect (i.e., association between lung cancer and ETS) and tests for exposure-response trend. In addition, the high-exposure data are analyzed alone to help minimize the effects of exposure misclassification resulting from the use of spousal smoking as a surrogate for ETS exposure. Various combining analyses also are performed to examine and compare the epidemiologic results for separate countries. Then several potential confounders and modifying factors are evaluated to determine if they affect the results. Finally, the studies are analyzed based on qualitative criteria. The studies are categorized into four tiers according to the utility of the study in terms of its likely ability to detect a possible effect, using specific criteria for evaluating the design and conduct as described in Appendix A. These tiers are integrated one at a time into statistical analyses, as an alternative method for evaluating the epidemiologic data that also takes into account qualitative considerations. Chapter 5 concludes with an overall weight-of-evidence determination for lung cancer based on the analyses in Chapters 3, 4, and 5.

In Chapter 6, the population risk for U.S. nonsmokers is characterized by estimating the annual number of lung cancer deaths that are attributable to exposure from all sources of ETS. The overall relative risk estimate from 11 U.S. epidemiological studies of passive smoking and lung cancer in female never-smokers is adjusted upward, based on body cotinine measurements from different U.S. population studies, to correct for the systematic downward bias caused by background exposure to ETS from sources other than spousal smoke. Additional assumptions are used to extend the results from female never-smokers to male never-smokers and long-term former smokers of both sexes. Separate estimates are calculated for background (workplace and other nonhome exposures) and spousal (home) exposures, as well as for female and male never-smokers and former smokers. An alternative analysis of the population risk is performed based solely on the Fontham et al. (1991) study, the only study that provides exposure-level

measurements. Chapter 6 also discusses the sources of uncertainty and sensitivity in the lung cancer estimates.

The final two chapters address passive smoking and noncancer respiratory disorders. Both the NRC and Surgeon General's reports concluded that children exposed to ETS from parental smoking are at greater risk for various respiratory illnesses and symptoms. This report confirms and extends those conclusions with analyses of more recent studies. New evidence for an association between ETS and middle ear effusion, and for a role of ETS in the cause as well as the prevalence and severity of childhood asthma, is reviewed. In addition, the evidence for an association between maternal smoking and SIDS is examined.

Chapter 7 reviews and analyzes epidemiologic studies of passive smoking and noncancer respiratory disorders, mainly in children. Possible biological mechanisms, additional risk factors and modifiers, and the potential long-term significance of early effects on lung function are discussed. Then, the evidence indicating relationships between childhood exposure to ETS and acute respiratory illnesses, middle ear disease, chronic respiratory symptoms, asthma, and lung function impairment, as well as between maternal smoking and SIDS, is evaluated.

Passive smoking as a risk factor for noncancer respiratory health effects in adults is also analyzed in Chapter 7. The NRC and Surgeon General's reports concluded that adults exposed to ETS may exhibit small deficits in lung function but noted that it is difficult to determine the extent to which ETS impairs respiration because so many other factors can similarly affect lung function. More recent evidence and new statistical techniques allow the demonstration of subtle effects of ETS on lung function and respiratory health in adults.

Chapter 8 discusses potential confounding factors and possible sources of bias in the ETS studies that might affect the conclusions of Chapter 7. Chapter 8 also describes methodological and data considerations that limit quantitative estimation of noncancer respiratory health effects attributable to ETS exposure. Finally, the chapter develops population impact assessments for ETS-attributable childhood asthma and for infant/toddler bronchitis and pneumonia. Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and early childhood, and an estimated 2 to 5 million children under age 18 are afflicted with asthma. Therefore, even small increases in individual risk for these illnesses can result in a substantial public health impact.

This chapter concludes that (1) MS, SS, and ETS are chemically similar and contain a number of known or suspected human carcinogens and toxic compounds; (2) marker compounds for ETS are measurable in a variety of indoor environments; (3) exposure to ETS is extensive; and (4) there is a measurable uptake of ETS by nonsmokers.

3.2. PHYSICAL AND CHEMICAL PROPERTIES

Over the past several years, there have been a number of reviews of the physical and chemical properties of mainstream and sidestream cigarette smoke (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). A particularly detailed review is contained in the recent book by Guerin et al. (1992). This section summarizes the findings of these reviews to identify the similarities and differences in mainstream and sidestream emissions and to establish that known and suspected human carcinogens and toxic agents are released into occupied spaces from tobacco combustion. Data contained in these reviews, as well as recently published material, are also presented to document that sidestream emissions of notable air contaminants result in measurable increases of these contaminants in indoor locations where individuals spend time.

The physical and chemical characterization of MS air contaminant emissions from cigarettes, cigars, or pipes is derived from laboratory-based studies that have typically utilized standardized testing protocols (FTC, 1990; Guerin et al., 1992). The data available are primarily for tobacco combustion in cigarettes and provide a substantial database on the nature of MS. These protocols employ smoking machines, set puff volumes and frequencies, and standardized air contaminant collection protocols (small chambers, Cambridge filters, chamber air flow rates, etc.). Existing standardized protocols reflect conditions representative of human smoking practices of over 30 years ago for nonfiltered cigarettes and may not reflect current human smoking parameters for today's filtered low-tar cigarettes (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). It has been suggested that current standardized protocols, particularly for filter cigarettes, may underestimate MS deliveries (Guerin et al., 1992). MS air contaminant emission rates determined in these studies using standardized protocols can be affected by a number of factors, such as puff volume, air dilution rate, paper porosity, filter ventilation air flow around the cigarette, and moisture content of the tobacco. Actual smoking habits of individuals can also dramatically alter the MS deliveries. Variability in any of the factors can affect the nature and quantity of the MS emissions.

Standardized testing protocols for assessing the physical and chemical nature of SS emissions from cigarette smoke do not exist, and data on SS are not as extensive as those for MS emissions. Protocols used for the generation and collection of SS emissions typically use standardized MS protocols (smoking machines, puff volumes, etc.) with modifications in the test

devices (use of small chambers) that allow for the simultaneous collection of SS emissions for analysis (Dube and Green, 1982; McRae, 1990; Rickert et al., 1984).

The protocols for the collection of SS emissions are such that results can be directly compared to MS emissions and thus provide valuable insights into the physical and chemical nature of ETS. It should be noted, however, that the SS emissions collected under these protocols may be somewhat different from ETS emissions. ETS also contains exhaled MS, which has not yet been characterized. Exhaled MS can contribute from 15% to 43% of the particulate matter in ETS, though little of the gas phase contaminants (Baker and Proctor, 1990). In addition, SS samples are not collected under conditions where the emissions are diluted and "aged," as is ETS. The aging and dilution of the SS emissions can produce changes in phase distribution of the contaminants.

Results of laboratory evaluations have indicated substantial similarities and some differences between MS and SS emissions from cigarettes (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). Differences in SS and MS emissions are due to differences in the temperature of combustion of the tobacco, Ph, and degree of dilution with air, which is accompanied by a corresponding rapid decrease in temperature. SS is generated at a lower temperature (approximately 600°C between puffs vs. 800-900°C for MS during puffs) and at a higher Ph (6.7-7.5 vs. 6.0-6.7) than MS. Being slightly more alkaline, SS contains more ammonia, is depleted of acids, contains greater quantities of organic bases, and contains less hydrogen cyanide than MS. Differences in MS and SS are also ascribable to differences in the oxygen concentration (16% in MS vs. 2% in SS). SS contaminants are generated in a more reducing environment than those in MS, which will affect the distribution of some compounds--nitrosamines, for example, are present in greater concentrations in SS than in MS.

SS is rapidly diluted in air, which results in a SS particle size distribution smaller than that for MS and in the potential for changes in phase distribution for several constituents. Nicotine, for example, while predominantly in the particle phase in MS, is found predominantly in the gas phase in ETS (Eudy et al., 1985). The shift to gas phase is due to the rapid dilution in SS. SS particle size is typically in the range of 0.01-1.0 μm, while MS particle size is 0.1-1.0 μm. The SS size distribution shifts to small sizes with increasing dilution (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Ingebrethsen and Sears, 1985). The differences in size distribution for MS and SS particles, as well as the different breathing patterns of smokers and nonsmokers, have implications for deposition of the produced particle contaminants in various regions of the respiratory tract. Estimates of from 47% to more than 90% deposition for MS and of 10% deposition for SS have been reported (U.S. DHHS, 1986).

Despite quantitative differences and potential differences in phase distributions, the air contaminants emitted in MS and SS are qualitatively very similar in their chemical composition because they are produced by the same process. Over 4,000 compounds have been identified in laboratory-based studies of MS (Dube and Green, 1982; Roberts, 1988). In a 1986 IARC monograph evaluating the carcinogenic risk of tobacco smoke to humans (IARC, 1986), 42 individual MS components were identified as carcinogenic in bioassays with laboratory animals, with many of these either known or suspected human carcinogens. Many additional compounds in MS have been identified as toxic compounds. Although SS emissions have not been chemically characterized as completely as MS emissions, many of the compounds found in MS emissions, including a host of carcinogenic agents, are found in SS emissions (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Dube and Green, 1982; Roberts, 1988) and at emission rates considerably higher than for MS.

Part of the data available from studies of MS and SS emissions is shown in Table 3-1 (extracted from NRC, 1986). These data are for nonfilter cigarettes and represent a summary of data from several sources. It is immediately obvious from Table 3-1 that SS and MS contain many of the same notable air contaminants, including several known or suspected human toxic and carcinogenic agents, and that SS emissions are often considerably higher than MS emissions. For the compounds shown in Table 3-1, all of the five known human carcinogens, nine probable human carcinogens, and three animal carcinogens are emitted at higher levels in SS than in MS, several by an order of magnitude or more. For example, *N*-nitrosodimethylamine, a potent animal carcinogen, is emitted in quantities 20 to 100 times higher in SS than in MS. Table 3-1 similarly shows that several toxic compounds found in MS are also found in SS (carbon monoxide, ammonia, nitrogen oxides, nicotine, acrolein, acetone, etc.). Again, for many of these compounds, SS emissions are higher than MS emissions--in some cases by an order of magnitude or higher.

The SS/MS emission ratios shown in Table 3-1 can be highly variable and potentially misleading because, as noted earlier, a number of factors can have a substantial impact on MS emissions. A filtered cigarette, for example, can substantially reduce MS of total mass well below that shown in Table 3-1, thus resulting in a much higher SS/MS ratio. A number of recent studies (Adams et al., 1987; Guerin, 1987; Higgins et al., 1987; Chortyk and Schlotzhauer, 1989; Browne et al., 1980; Guerin et al., 1992) indicate that, quantitatively, SS emissions show little variability as a function of a number of variables (puff volume, filter vs. nonfilter cigarette, and filter ventilation). The lack of substantial variability in SS emissions is related to the fact that sidestream emissions are primarily related to the weight of tobacco and paper consumed during

Table 3-1. Distribution of constituents in fresh, undiluted mainstream smoke and diluted sidestream smoke from nonfilter cigarettes[1]

Constituent	Amount in MS	Range in SS/MS
Vapor phase:[2]		
Carbon monoxide	10-23 mg	2.5-4.7
Carbon dioxide	20-40 mg	8-11
Carbonyl sulfide	12-42 μg	0.03-0.13
Benzene[3]	12-48 μg	5-10
Toluene	100-200 μg	5.6-8.3
Formaldehyde[4]	70-100 μg	0.1-~50
Acrolein	60-100 μg	8-15
Acetone	100-250 μg	2-5
Pyridine	16-40 μg	6.5-20
3-Methylpyridine	12-36 μg	3-13
3-Vinylpyridine	11-30 μg	20-40
Hydrogen cyanide	400-500 μg	0.1-0.25
Hydrazine[4]	32 ng	3
Ammonia	50-130 μg	3.7-5.1
Methylamine	11.5-28.7 μg	4.2-6.4
Dimethylamine	7.8-10 μg	3.7-5.1
Nitrogen oxides	100-600 μg	4-10
N-Nitrosodimethylamine[4]	10-40 ng	20-100
N-Nitrosodiethylamine[4]	ND-25 ng	<40
N-Nitrosopyrrolidine[4]	6-30 ng	6-30
Formic acid	210-490 μg	1.4-1.6
Acetic acid	330-810 μg	1.9-3.6
MethCyl chloride	150-600 μg	1.7-3.3
1,3-Butadiene[4,6]	69.2 μg	3-6

(continued on the following page)

Table 3-1. (continued)

Constituent	Amount in MS	Range in SS/MS
Particulate phase:[2]		
Particulate matter[7]	15-40 mg	1.3-1.9
Nicotine	1-2.5 mg	2.6-3.3
Anatabine	2-20 μg	<0.1-0.5
Phenol	60-140 μg	1.6-3.0
Catechol	100-360 μg	0.6-0.9
Hydroquinone	110-300 μg	0.7-0.9
Aniline[4]	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine[3]	1.7 ng	30
4-Aminobiphenyl[3]	4.6 ng	31
Benz[a]anthracene[5]	20-70 ng	2-4
Benzo[a]pyrene[4]	20-40 ng	2.5-3.5
Cholesterol	22 μg	0.9
γ-Butyrolactone[5]	10-22 μg	3.6-5.0
Quinoline	0.5-2 μg	3-11
Harman[8]	1.7-3.1 μg	0.7-1.7
N-Nitrosonornicotine[5]	200-3,000 ng	0.5-3
NNK[9]	100-1,000 ng	1-4
N-Nitrosodiethanolamine[4]	20-70 ng	1.2
Cadmium[4]	110 ng	7.2
Nickel[3]	20-80 ng	13-30
Zinc	60 ng	6.7
Polonium-210[3]	0.04-0.1 pCi	1.0-4.0
Benzoic acid	14-28 μg	0.67-0.95
Lactic acid	63-174 μg	0.5-0.7
Glycolic acid	37-126 μg	0.6-0.95
Succinic acid	110-140 μg	0.43-0.62
PCDDs and PCDFs[10]	1 pg	2

(continued on the following page)

Table 3-1. (continued)

[1]Data in this table come from the NRC report (1986), except where noted, which compiled data from Elliot and Rowe, 1975; Schmeltz et al., 1979; Hoffman et al., 1983; Klus and Kuhn, 1982; Sakuma et al., 1983, 1984a, 1984b; and Hiller et al., 1982. Full references are given in NRC, 1986. Diluted SS is collected with airflow of 25 mL/s, which is passed over the burning cone; as presented in the NRC report on passive smoking (1986).
[2]Separation into vapor and particulate phases reflects conditions prevailing in MS and does not necessarily imply same separation in SS.
[3]Known human carcinogen, according to U.S. EPA or IARC.
[4]Probable human carcinogen, according to U.S. EPA or IARC.
[5]Animal carcinogen (Vainio et al., 1985).
[6]Data from Brunnemann et al., 1990.
PCDDs = polychlorinated dibenzo-p-dioxins;
PCDFs = polychlorinated dibenzofurans.
[7]Contains di- and polycyclic aromatic hydrocarbons, some of which are known animal carcinogens.
[8]1-methyl-9*H*-pyrido[3,4-*b*]-indole.
[9]NNK = 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone.
[10]Data from Löfroth and Zebühr, 1992. Amount is given as International Toxic Equivalent Factor (I-TEF).

the smoldering period, with little influence exerted by cigarette design (Guerin et al., 1992). More recent summary data on SS emission rates from filtered test cigarettes and commercial cigarettes for many compounds of human health interest are presented by Guerin et al. (1992) and shown, with modifications, in Table 3-2. Much of the data in Table 3-2 is extracted from detailed data presented in an R.J. Reynolds (1988) report. Table 3-2, like Table 3-1, documents that appreciable quantities of important air contaminants are emitted into the air from SS emissions resulting from tobacco combustion. The table demonstrates that SS emissions are reasonably similar across different brands of cigarettes, varying by only a factor of 2-3. So, while MS emissions can vary considerably (Table 3-1), SS emissions are relatively constant (Table 3-2).

In summary, the available data indicate that tobacco combustion results in the emission of a large number of known toxic compounds and that many of these will be released at rates that are higher in SS than in MS. Emphasis in characterizing SS emissions has been placed upon those carcinogens and toxic compounds found in MS. Although not all of the SS emissions have been characterized, the available data showing SS to be enriched in many of the same carcinogens and toxic agents found in MS lead to the conclusion that ETS will contain the same hazardous compounds. This conclusion provides the basis for the toxicological comparison of these complex mixtures in Chapter 4. The enrichment of several known or suspected carcinogens in SS relative to MS suggests that the SS contaminant mix may be even more carcinogenic than the MS mix, per

Table 3-2. Example sidestream cigarette smoke deliveries[1]

Constituent	Kentucky reference[2]	Commercial
	Milligrams per cigarette	
Condensate		36-67
Total particulate matter	16.9	16-36, 20-23
Nicotine	5.6	5.7-11.2, 2.7-6.1
Carbon monoxide	54	41-67
Carbon dioxide	474	
Nitrogen oxides	0.9	
Ammonia	9.1	
Formaldehyde	0.7	
Acetaldehyde	4.2	
Acrolein	1.3, 1.4	0.7-1.0
Propionaldehyde	0.9	
Benzene	0.3, 0.4, 0.7	0.3-0.5
Toluene	0.8, 1.3	0.8-1.1
Styrene		
Pyrrole	0.4	
Pyridine	0.3	
3-Vinylpyridine		
3-Hydroxypyridine		
Limonene	0.3	<0.1-0.4
Neophytadiene		0.1-0.2
Isoprene	2.5, 6.1	4.4-6.5
nC_{27}-nC_{33}	0.2-0.8	
Acetonitrile	1.0, 0.8[3]	
Acrylonitrile	0.2	

(continued on the following page)

Table 3-2. (continued)

Constituent	Kentucky reference[2]	Commercial
	Micrograms per cigarette	
Hydrogen cyanide	53, 17[3]	
Phenol		44-371
o-Cresol		24-98
m + p-Cresol		59-299
Catechol		46-189
Hydroquinone		26-256
Naphthalene		53-177
Phenanthrene		2.4
Anthracene		0.7
Fluoranthene		0.7
Pyrene		0.5
Benz[a]anthracene	0.2	0.2
Benzo[a]pyrene	0.1	0.1
NNN[4]	0.2	1.7
NNK[4]	0.4	0.4
NAT[4]	0.1	
NAB[4]	<0.1	
DMNA[4]	0.3	0.7-1.0
EMNA[4]		<0.1
DENA[4]		<0.1-0.1
NPYR[4]	0.2	0.2-0.4
2-Naphthylamine		<0.1-1[5]
4-Aminobiphenyl		<0.1-0.2[5]
Nickel		
Cadmium		
Lead		
Chromium		

(continued on the following page)

Table 3-2. (continued)

[1]Table reprinted from Guerin et al. 1992, who compiled data from Browne et al., 1990; Brunnemann et al., 1977, 1978, and 1990; Chortyk and Schlotzhauer, 1989; Grimmer et al., 1987; Guerin, 1991; Higgins et al., 1987; Johnson et al., 1973; O'Neill et al., 1987; R.J. Reynolds, 1988; Rickert et al., 1984; Sakuma et al., 1983, 1984a, 1984b; and Norman et al., 1983. Full references are given in Guerin et al., 1992.
[2]Filter 1R4F unless otherwise specified.
[3]Nonfilter 1R1.
[4]*N*-nitrosonornicotine (NNN), 4-methylnitrosoamino-1-(3-pyridinyl)-1-butanone (NNK), *N*-nitrosoanatabine (NAT), *N*-nitrosoanabasine (NAB), dimethylnitrosamine (DMNA), ethylmethylnitrosamine (EMNA), diethylnitrosamine (DENA), *N*-nitrosopyrrolidine (NPYR).
[5]Calculated from NRC, 1986, SS/MS ratio.

unit tobacco burned. The mouse skin painting bioassays of organic extracts of MS and SS reviewed in Chapter 4 add support to the suggestion that SS is a more potent carcinogen than MS. Furthermore, the incomplete chemical characterization of SS emissions means that there may be additional, as yet unidentified compounds in SS of human health interest.

Detailed chemical characterizations of ETS emissions under conditions more typical of actual smoking conditions (e.g., using smokers rather than smoking machines) are limited. As a result, the impact on ETS of factors such as the rapid dilution of SS emissions, adsorption and remission of contaminants, and exhaled MS is not well understood. Several studies conducted in chambers or controlled environments and using smokers (e.g., Benner et al., 1989; Duc and Huynh, 1989; Leaderer and Hammond, 1991; R.J. Reynolds, 1988; NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992) have characterized some of the ETS components (total mass, carbon monoxide, nicotine and other selected compounds, including known carcinogenic and toxic substances). These studies indicate that many of the contaminants of interest in SS are measurable in ETS (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992) and that several SS contaminants (e.g., total mass, carbon monoxide, nicotine) are easily measurable in ETS. It is not known how the MS and SS air contaminant emission data for specific compounds, generated by the standardized testing protocols utilized, compare to data gathered under conditions more representative of actual smoking in occupied spaces.

3.3. ASSESSING ETS EXPOSURE

In the course of a typical day, an individual spends varying amounts of time in a variety of environments (residences, industrial and nonindustrial workplaces, automobiles, public access buildings, outdoors, etc.). While in these different environments, individuals are exposed to a

broad and complex spectrum of organic and inorganic chemicals in gaseous and particle forms, as well as a range of viable particles.

ETS is a major source of indoor air contamination because of the large, though decreasing, number of smokers in the population and the quantity and quality of the contaminants emitted into the environment from tobacco combustion (NRC, 1981, 1986). In a 1990 self-reported smoking survey of a representative sample of the U.S. civilian, noninstitutionalized population, it was reported that 50.1% (89.9 million) of the adult population were ever-smokers and 25.5% were current smokers (CDC, 1992). The reported average number of cigarettes smoked per day was 19.1, with 22.9% of smokers reporting smoking 25 or more cigarettes per day. From 1965 through 1985, the overall smoking prevalence among U.S. adults declined 0.5% annually, with a 1.1% annual decline between 1987 and 1990.

In another recent survey (CDC, 1991b), 40.3% (46 million) of employed adults ($\geq$ 18 years old) in 1988 (who reported that their workplace was not in their home) worked in locations where smoking was allowed in designated or other areas. Of the nonsmokers (79.2 million), 36.5% (28.5 million) worked at places that permitted smoking in designated (if any) and other areas. Of these nonsmokers, 59.2% (16.9 million) reported that exposure to ETS in their workplace caused them discomfort. The survey highlighted the importance of the workplace as a major source of ETS exposure in addition to the home.

The available data on ETS exposure to children in the home are limited. However, based on the 1988 National Health Interview Survey on Child Health, 42% of children 5 years of age and under are estimated to live in households with current smokers (Overpeck and Moss, 1991). The home environment is clearly an important source of ETS exposure for children.

Nationally based survey data needed to make direct estimates of the frequency, magnitude, and duration of ETS exposure for nonsmoking adults and children and the different indoor environments in which those exposures occur are not available. The survey data available, however, do indicate that due to the ubiquitous nature of ETS in indoor environments, some unintentional inhalation of ETS by nonsmokers is unavoidable.

The combustion of tobacco results in the emission of a particularly complex array of air contaminants into indoor microenvironments. Data on the chemical composition of mainstream and sidestream cigarette emissions as well as measurements in indoor spaces where smoking occurs indicate that exposure to ETS will result in exposure to toxic and carcinogenic agents (Section 3.2). The nature of the ETS contaminant mix and eventual human exposure is the product of the interaction of several interrelated factors associated with the source, transport, chemical transformation, dispersal, removal, and remission from surfaces, as well as human activities. Efforts to determine adverse health effects of ETS must address the issue of exposure to a

complex mixture, which can occur in a number of environments. Assessing exposure to ETS, as with any complex air contaminant mix, is inherently complicated in epidemiologic studies (Leaderer et al., 1992).

Because of the many potentially toxic agents in ETS and the various possible toxicological endpoints of interest, it is neither feasible nor desirable to focus on any one contaminant. Rather, the focus is on gathering information on marker or proxy compounds or other indicators of ETS exposure. In assessing these exposures, both direct and indirect methods can be employed. Direct methods include personal monitoring and measurement of biological markers. Indirect methods employ models to estimate exposures. The modeling approach generally makes use of stationary monitoring and questionnaire data.

Stationary monitoring is used to measure concentrations of air contaminants in different environments. These measured concentrations are then combined with time-activity patterns (time budgets) to determine the average exposure of an individual as the sum of the concentrations in each environment weighed by the time spent in that environment. Monitoring of contaminants might also be supplemented with the monitoring of factors in the environment that affect the contaminant levels measured (meteorological variables, primary compounds, ventilation, etc.). Measurement of these factors, in a carefully chosen set of conditions, can lead to models that predict concentrations in the absence of measured concentrations and provide a means of assessing the impact of efforts to reduce or eliminate exposures. Questionnaires are used to determine time-activity patterns of individuals, to provide a simple categorization of potential exposure, and to obtain information on the properties of the environment affecting the measured levels (number of smokers, amounts smoked, etc.).

ETS exposure measurements, whether conducted to support epidemiological studies or to determine the extent of exposure in nonsmoking individuals, have typically employed air monitoring of indoor spaces, personal monitoring, and questionnaires. Modeling of ETS exposures, while useful in estimating, from measured data, the level of exposure in a variety of indoor spaces under varying conditions, is beyond the scope of this report.

3.3.1. Environmental Concentrations of ETS

The SS emission data discussed in Section 3.2 and shown in Tables 3-1 and 3-2 clearly indicate that tobacco combustion will result in the release of thousands of air contaminants into the environments in which smoking occurs. The concentrations of the known and unidentified contaminants in the ETS complex mix in an enclosed space can exhibit a pronounced spatial and temporal distribution. The concentration is the result of a complex interaction of several important variables, including (1) the generation rate of the contaminant(s) from the tobacco

(including both SS and exhaled MS emissions), (2) location in the space that smoking occurs, (3) the rate of tobacco consumption, (4) the ventilation or infiltration rate, (5) the concentration of the contaminant(s) in the ventilation or infiltration air, (6) air mixing in the space, (7) removal of contaminants by surfaces or chemical reactions, (8) re-emission of contaminants by surfaces, and (9) the effectiveness of any air cleaners that may be present. Additional considerations relate to the location at which contaminant measurements are made, the time of sample collection, the duration of sampling, and method of sampling.

Variations in any one of the above factors related to introduction, dispersal, and removal of ETS contaminants can have a marked impact on the resultant indoor ETS constituent concentrations. Any one of these parameters can vary by an order of magnitude or more. For example, infiltration rates in residences can range from 0.1 to over 2.0 air changes per hour, and house volumes can range from 100 to over 700 m^3 (Grimsrud et al., 1982; Grot and Clark, 1979; Billick et al., 1988; Koutrakis et al., 1992). Smoking rates and mixing within and between rooms can also show considerable variability. The potential impact on indoor ETS-related respirable suspended particle (RSP) mass concentrations due to variations in these parameters is demonstrated in Figures 3-1 and 3-2 (these figures were taken directly from Figures 5-4 and 5-5 in NRC, 1986). Figures 3-1 and 3-2 are based on the mass balance model for ETS (NRC, 1986) for a typical range of input parameters encountered in indoor spaces. These figures demonstrate that ETS-generated RSP concentrations in indoor environments can range from less than 20 $\mu g/m^3$ to over 1 mg/m^3 depending upon the location and conditions of smoking.

Numerous field studies in "natural" environments have been conducted to assess the contribution of smoking occupancy to indoor air quality. These studies, summarized in a number of reviews (e.g., NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992), have measured several ETS-related contaminants of human health concern (e.g., particle mass, carbon monoxide, benzene, nicotine, polycyclic aromatic hydrocarbons, *N*-nitrosamines), in a number of enclosed environments (e.g., residential, office, transportation) and under a variety of smoking and ventilation rates. These studies demonstrate that (1) many of the contaminants of health interest found in SS are also found in ETS; (2) ETS contaminants are found above background level in a wide range of indoor environments in which smoking occurs; and (3) the concentrations of ETS contaminants indoors can be highly variable. These findings can be demonstrated for selected ETS-related compounds presented in Figure 3-3 and in Table 3-3.

Figure 3-3 principally utilizes data summaries presented in reviews of indoor measurements of ETS-related compounds in a variety of indoor spaces (NRC, 1986; U.S. DHHS, 1986; and particularly Guerin et al., 1992). Only the range of average concentrations measured in

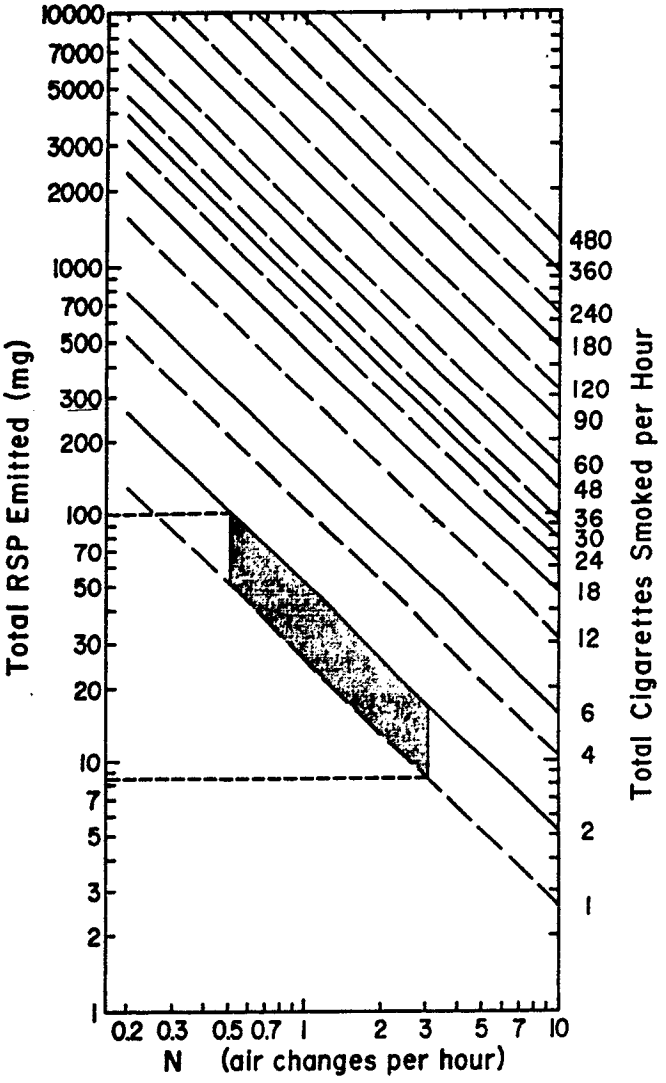


Figure 3-1. Diagram for calculating the respirable suspended particle mass (RSP) from ETS emitted into any occupied space as a function of the smoking rate and removal rate (N). The removal rate is equal to the sum of the ventilation or infiltration rate (n_v) and the removal rate by surfaces (n_s) times the mixing factor. The calculated ETS-related RSP mass determined from this figure serves as an input to Figure 3-2 to determine the ETS-related RSP mass concentration in any space in $\mu g/m^3$. Smoking rates (diagonal lines) are given as cigarettes smoked per hour. Mixing is determined as a fraction, and n_v and n_s are in air changes per hour (ach). All three parameters have to be estimated or measured. Calculations were made using the equilibrium form of the mass-balance equation and assume a fixed emission rate of 26 mg/m^3 of RSP.

Shaded area shows the range of RSP emissions that could be expected for a residence with one smoker smoking at a rate of either 1 or 2 cigarettes per hour for the range of mixing, ventilation, and removal rates occurring in residences under steady-state conditions.

Source: NRC, 1986.

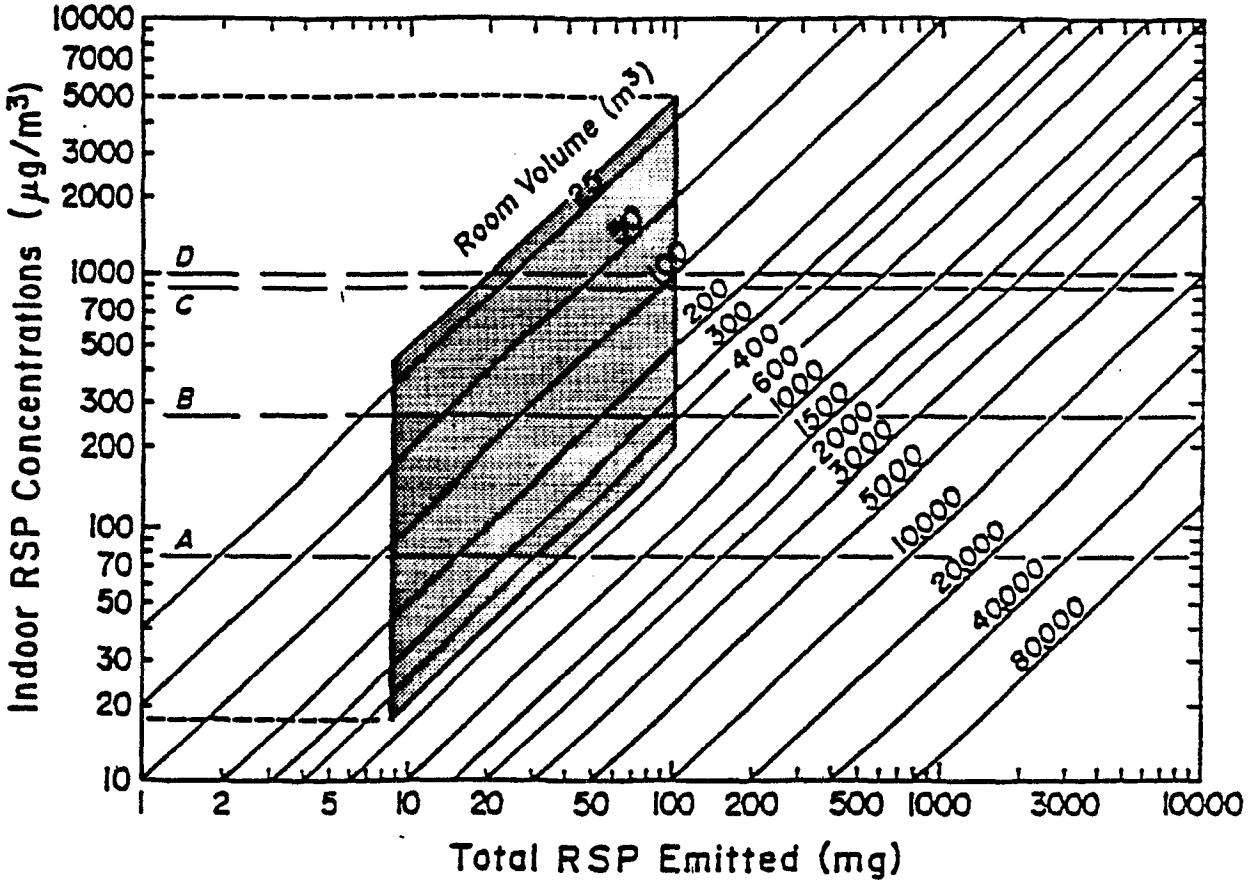


Figure 3-2. Diagram to calculate the ETS-associated respirable suspended particle mass (RSP) concentration in $\mu g/m^3$ in a space as a function of total mass of ETS-generated RSP emitted in mg (determined from Figure 3-1) and the volume of a space (diagonal lines). The concentrations shown assume a background level of zero in the space. The particle concentrations shown are estimates during smoking occupancy. The dashed horizontal lines (A, B, C, and D) refer to National Ambient Air Quality Standards (health-related) for total suspended particulates established by the U.S. Environmental Protection Agency. A is the annual geometric mean. B is the 24-hour value not to be exceeded more than once a year. C is the 24-hour air pollution emergency level. D is the 24-hour significant harm level. Shaded area shows the range of concentrations expected (from Figure 3-1) for a range of typical volumes of U.S. residences and rooms in these residences.

Source: NRC, 1986.

Range of Average Indoor Concentrations of Noteable ETS Contaminants Associated with Smoking Occupancy

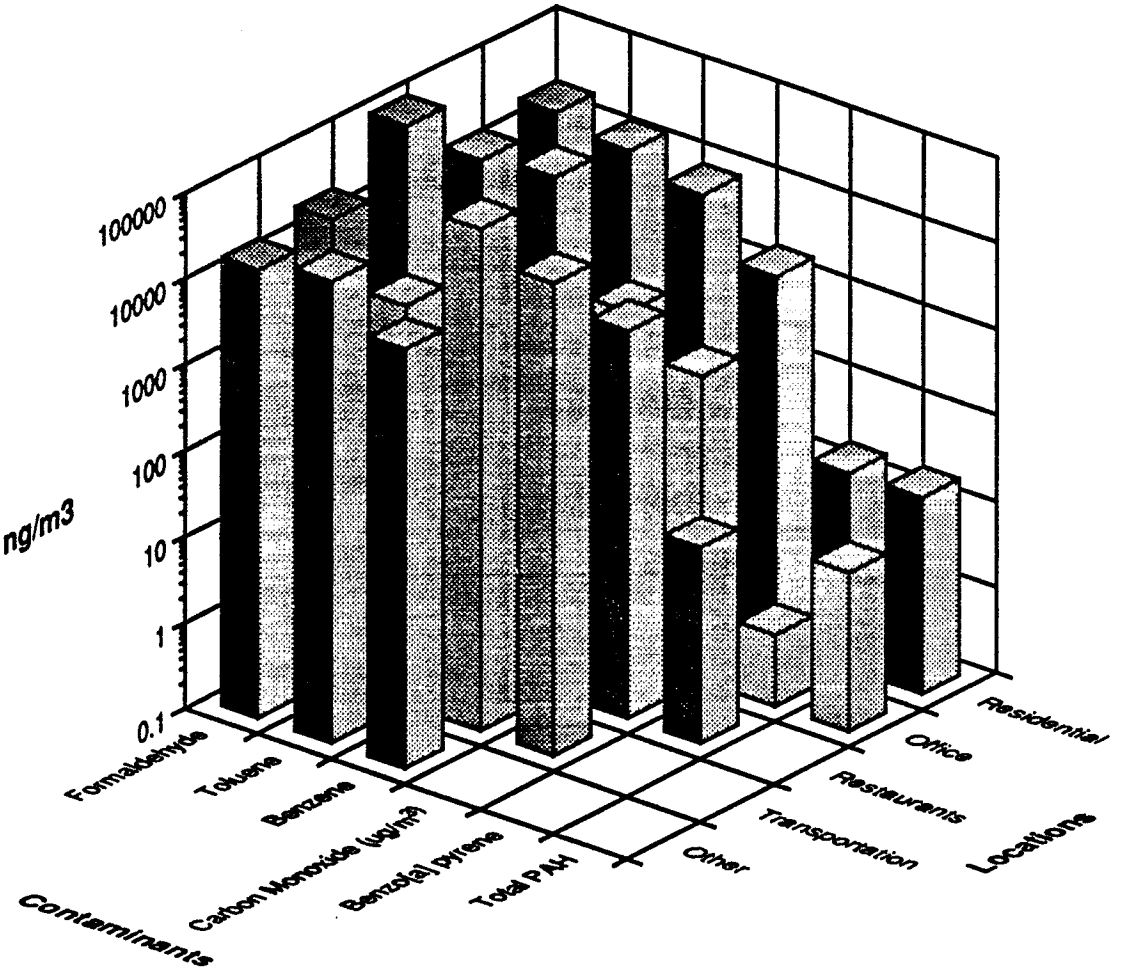


Figure 3-3. Range of average indoor concentrations for notable ETS contaminants associated with smoking occupancy for different indoor environments. Ranges of averages are principally from tables presented in Guerin et al. (1992), although other sources were used (NRC, 1986; U.S. DHHS, 1986; Turk et al., 1987). Background levels are subtracted. Maximum recorded values are typically orders of magnitude higher than averages shown.

Table 3-3. Tobacco-specific *N*-nitrosamines in indoor air (ng/m³)[1]

Site	Approx. # of cigarettes smoked	Collection time (hours)	Flow rate (liters/ min.)	Tobacco-specific *N*-nitrosamines		
				NNN[2]	NAT[2]	NNK[2]
Bar I	25-35	3	3.2	22.8	9.2	23.8
Bar II	10-15	3	3.2	8.3	6.2	9.6
Bar III	10-15	3	3.2	4.3	3.7	11.3
Restaurant[3]	25-30	6	2.15	1.8	1.5	1.4
Restaurant[3]	40-50	8	2.1	ND	ND	3.3
Car[4]	13	3.3	2.15	5.7	9.5	29.3
Train I	50-60	5.5	3.3	ND	ND	4.9
Train II	50-60	6	3.3	ND	ND	5.2
Office	25	6.5	3.3	ND	ND	26.1
Smoker's Home	30	3.5	3.3	ND	ND	1.9

[1]Data corrected for recovery.
[2]NNN = NNN-*N*-nitrosonornicotine; NAT = NAT-*N*-nitrosoanataline;
NNK = NNK-4-methylnitrosoamino-1-(3 pyridinyl)-1-butanone.
[3]Smoking section.
[4]Windows partially open.
ND = not detected (in some cases due to chromatographic interference).

Source: Brunnemann et al., 1992.

different environments is shown. Maximum values, which can range up to two or more orders of magnitude above the averages, are not shown in Figure 3-3. Background levels for nonsmoking conditions have been subtracted. When smoking occurs, concentrations of total polycyclic aromatic hydrocarbons, benzo[a]pyrene, benzene, formaldehyde, toluene, and carbon monoxide will be elevated above background levels in a variety of indoor environments. Figures 3-7 and 3-8 present a similar summary with the same conclusions for two other ETS-related contaminants--respirable suspended particle mass and nicotine.

N-nitrosamines are important constituents of SS because they are considered to be carcinogenic, because they are emitted in much larger quantities in SS than in MS (Table 3-1), and because tobacco combustion is the only identified air source in the nonoccupational indoor environment. Guerin et al. (1992) reviewed the available data on indoor levels of *N*-nitrosamines

related to smoking occupancy. They concluded that levels associated with smoking can range from less than detectable to as high as 100 ng/m^3 for nitrosodimethylamine (NDMA) under conditions of heavy smoking. A more typical range of concentrations of NDMA were < 10-40 ng/m^3. In a recent paper, Brunnemann et al. (1992) demonstrated that exposure to tobacco specific *N*-nitrosamines can occur in a variety of indoor spaces under a range of smoking conditions (Table 3-3).

The potential for high exposures of nonsmokers to carcinogenic components found enriched in SS can be demonstrated in the case of 4-aminobiphenyl (4-ABP). Tables 3-1 and 3-2 show 4-ABP emissions in SS to be approximately 30 times higher than in MS (100-200 μg/cig). Despite the fact that SS emissions of 4-ABP are diluted rapidly in the indoor environment, presumably resulting in considerably less exposure than to smokers, 4-ABP Hb adduct levels in nonsmokers have been found to be 10% to 20% of those in smokers (see Section 3.3.2).

There are important circumstances where concentrations of ETS-related contaminants in indoor spaces may considerably underestimate potential levels of exposure. These circumstances occur when the SS emissions or exhaled MS emissions are in direct proximity to a nonsmoker (e.g., an infant held by a smoking mother or father, or when a nonsmoker is directly downwind of the plume of a smoldering cigarette). While there are no measurements to assess the impact on the nonsmoker's exposure under these conditions, it is an important exposure and will be much higher than would be predicted from existing environmental measurements of more diluted SS and exhaled MS emissions.

The data discussed above represent concentrations measured in selected indoor environments and indicate that exposure will occur for individuals in those spaces. Estimating the actual level of exposure (concentration × time) requires knowledge of the actual time spent in those environments.

3.3.1.1. *Markers for Environmental Tobacco Smoke*

Although ETS is a major source of indoor air contaminants, the actual contribution of ETS to indoor air is difficult to assess due to the background levels of many contaminants contributed from a variety of other indoor and outdoor sources. Relatively few of the individual constituents of the ETS mix have been identified and characterized. In addition, little is known about the role of individual ETS constituents in eliciting the adverse health and nuisance effects observed. However, the issue is not how to fully characterize the exposure to each ETS-related contaminant, but rather how to obtain accurate quantitative measures of exposure to the entire ETS mixture. The measurement of all components in ETS is not feasible, practical, or even desirable due to

limitations in knowledge of the mixture components related to the effects of interest, as well as the feasibility and cost of sampling. It is necessary then to identify a marker (also referred to as a tracer, proxy, indicator, or surrogate) for ETS that will, when measured, accurately represent the frequency, duration, and magnitude of exposure to ETS. These markers can be chemicals measured in the air, biomarkers, models, or simple questionnaires.

There are important issues related to the measurement of a given marker compound to represent exposure to ETS. Ideally, an air contaminant marker for ETS should (1) vary with source strength, (2) be unique to the source, (3) be easily detected in air at low concentrations, (4) be similar in emission rates for a variety of tobacco products, (5) occur in a consistent ratio in air to other ETS components in the complex mix, and (6) be easily, accurately, and cost effectively measured (Leaderer, 1990). The marker can be a specific compound (e.g., nicotine) or much less specific (e.g., respirable suspended particle mass). These criteria for selecting a suitable marker compound are the ideal criteria. In practice, no single contaminant or class of contaminants has been identified that would meet all the criteria. Selection of a suitable marker for ETS is reduced to satisfying as many of the criteria for judging a marker as is practical. In using a marker, it is important to state clearly the role of the marker and to note its limitations.

A number of marker or proxy compounds have been used to represent ETS concentrations in both field and chamber studies. Nicotine, carbon monoxide, 3-ethenylpyridine, nitrogen dioxide, pyridine, aldehydes, nitrous acid, acrolein, benzene, toluene, myosmine, and several other compounds have been used or suggested for use as markers or proxies for the vapor phase constituents of ETS (NRC, 1986; U.S. DHHS, 1986; Hammond et al., 1987; Eatough et al., 1986; Löfroth et al., 1989; Leaderer and Hammond, 1991; Guerin et al., 1992). Tobacco-specific nitrosamines, particle phase nicotine and cotinine, solanesol, polonium-210, benzo[a]pyrene, potassium, chromium, and respirable suspended particle mass (RSP--particle mass ≤ 2.5 μm) are among the air contaminants used or suggested for use as markers for particle phase constituents of ETS (NRC, 1986; U.S. DHHS, 1986; Leaderer and Hammond, 1991; Benner et al., 1989; Hammond et al., 1987; Rickert, 1984; Guerin et al., 1992). All the markers employed to date have some problems associated with their use. For example, carbon monoxide, nitrogen oxides, benzene, and RSP have many indoor and outdoor sources other than the combustion of tobacco, while other compounds such as nitrosamines and benzo[a]pyrene are sufficiently difficult to measure (e.g., concentrations in smoking environments are low and the cost of collection and analysis of samples is high) that their use is very limited.

At the present time, vapor phase nicotine and respirable suspended particulate matter are widely and most commonly used as markers of the presence and concentration of ETS for a

variety of reasons associated with their ease of measurement, existing knowledge of their emission rates from tobacco combustion, and their relationship to other ETS contaminants.

Vapor phase nicotine, the dominant form of nicotine in ETS (Eudy et al., 1985; NRC, 1986; U.S. DHHS, 1986; Hammond et al., 1987; Eatough et al., 1986; Guerin et al., 1992) accounts for approximately 95% of the nicotine in ETS and is a good marker air contaminant for ETS. It is specific to tobacco combustion and is emitted in large quantities in ETS (NRC, 1981, 1986; U.S. DHHS, 1986; Rickert et al., 1984; Eatough et al., 1990; Guerin et al., 1992). Chamber measurements have shown that nicotine concentrations vary with source strength (Rickert et al., 1984; Hammond et al., 1987; Hammond and Leaderer, 1987; Leaderer and Hammond, 1991) and show little variability among brands of cigarettes, despite variations in MS emissions (Rickert et al., 1984; Leaderer and Hammond, 1991). Field studies have shown that weekly nicotine concentrations are highly correlated with the number of cigarettes smoked (Hammond et al., 1987; Mumford et al., 1989; Thompson et al., 1989; Leaderer and Hammond, 1991). One large field study (Leaderer and Hammond, 1991) showed that weekly nicotine concentrations were strongly correlated with measured RSP levels, as well as with reported number of cigarettes smoked. In this study, the slope of the regression line was 10.8 (standard error of $\pm$ 0.72), similar to the RSP/nicotine level seen in chamber studies. Also, the RSP intercept was equal to background levels in homes without smoking (17.9 $\mu g/m^3$ $\pm$ 1.63) (Leaderer et al., 1990). A comparable study by Miesner et al. (1989) of particulate matter and nicotine in workplaces found a similar ratio between RSP and nicotine. The utility of nicotine as an ETS marker is enhanced by the fact that recent advances in air sampling have resulted in the development of a variety of validated and inexpensive passive and active monitoring methods for measuring nicotine in indoor air environments and for personal monitoring (Hammond et al., 1987; Hammond and Leaderer, 1987; Eatough et al., 1989a; Koutrakis et al., 1989; Muramatsu et al., 1984; Oldaker and Conrad, 1987).

Nicotine is also an attractive marker for the complex ETS air contaminant mix because it and its metabolites, principally cotinine, can serve as biomarkers of ETS exposure. Nicotine and cotinine have long served as markers for active smoking. Over the past several years, measurements of nicotine and cotinine in blood, urine, and saliva have been used extensively as reasonably sensitive biomarkers indicative of exposure to ETS (see Section 3.3.2).

Nicotine is, however, not an ideal ETS marker. One of the potential drawbacks is that vapor-phase nicotine has a high affinity for indoor surfaces. The high adsorption rate of nicotine could decrease its concentration relative to other ETS constituents, particularly ETS-associated particle mass (Eudy et al., 1986; Rickert et al., 1990; Eatough et al., 1989b). This relative decrease in concentration could lead to an underestimation of ETS exposures. The ratio of nicotine to RSP and possibly other ETS constituents would be expected to be most dynamic as the ETS

contaminant mix ages (Eatough et al., 1989a). An additional potential problem is that nicotine may be re-emitted from interior surfaces, resulting in measurable concentrations in the absence of active smoking. There have, however, been a number of field studies (see above and Figures 3-4 and 3-7) where nicotine has been used successfully as an ETS marker. These studies would indicate that the uncertainties associated with nicotine in typical indoor environments under normally encountered smoking rates are relatively small. Levels of nicotine in smoking environments have been measured over several orders of magnitude (Figures 3-4 and 3-7), suggesting that the uncertainty associated with its high adsorption rate is small compared to the concentration range. It should also be noted that other gas phase ETS contaminants may exhibit adsorption and reemission properties similar to that of nicotine. Use of nicotine or any other ETS marker must consider the limitations associated with its use.

The combustion of tobacco results in substantial emissions of RSP. One small chamber study using a smoking machine found the average particle emission rate for 15 Canadian cigarettes to be 24.1 mg/cigarette with a range of 15.8-36.0 mg/cigarette (Rickert et al., 1984). A large chamber study using smokers reported an average particle emission rate of 17.1 mg for 12 brands of American cigarettes (Leaderer and Hammond, 1991). This study noted that emission rates among brands are similar. Included in the RSP are a number of compounds of direct health concern, e.g., many of the polycyclic aromatic hydrocarbons and tobacco-specific *N*-nitrosamines (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Tables 3-1 and 3-3, Figure 3-3). There are a number of accepted methods to measure personal RSP exposures and concentrations in indoor environments (Ogden et al., 1990). The available methods permit the accurate measurement of RSP for sampling times ranging from seconds to several days.

Numerous studies of personal exposures to RSP and of RSP levels in indoor environments have shown elevated levels of RSP in environments where smoking was reported (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Leaderer and Hammond, 1991; Turk et al., 1987). One study found a strong correlation between weekly residential RSP levels and reported number of cigarettes smoked (Leaderer and Hammond, 1991). At low smoking and high ventilation rates, however, it may be difficult to separate out the ETS-associated RSP in a background of RSP from other indoor sources (e.g., kerosene heaters) or even from outdoor sources. In using RSP as a marker for ETS, it is important to account for the background RSP level related to other sources before ascertaining the contribution from ETS. Efforts to model ETS exposures for the purpose of assessing risks and the impact of various mitigation measures have often focused on predicting ETS-associated RSP concentrations (e.g., Repace and Lowrey, 1980).

3.3.1.2. *Measured Exposures to ETS-Associated Nicotine and RSP*

3.3.1.2.1. *Measurements using stationary monitors.* In the past several years, numerous studies have been conducted in a variety of indoor environments to determine the impact of tobacco combustion on levels of nicotine and RSP. These studies have employed a variety of protocols that used a diversity of air sampling techniques (passive, active, continuous integrative, etc.), sampled over highly varying timeframes (from minutes to several days), and collected highly variable information on factors affecting the measured concentrations (number of cigarettes smoked, volume of building, ventilation rates, etc.). In an attempt to present an overall view of the contribution of ETS to indoor air quality, only the summary results of the measured concentrations of ETS-associated nicotine and RSP will be discussed here. Several reviews of the studies evaluating the impact of ETS on indoor RSP levels have been conducted over the past few years, and a number of recent reports have discussed measured indoor levels of nicotine (e.g., NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Leaderer and Hammond, 1991). Only the indoor levels measured are discussed and summarized. In order to assess exposures, the time in contact with the concentrations would have to be estimated or measured. The reader is referred to those reports and to the individual study reports to acquire more detailed information.

Measured nicotine concentrations in various indoor environments where smoking was noted are summarized in Figure 3-4. The mean concentration, standard deviation, and the maximum and minimum values recorded are presented. Also given in Figure 3-4 are the number of locations in which the measurements were taken and the references in which the data were reported. Elevated nicotine levels were measured in all microenvironments in which smoking was reported. Measured nicotine levels, as would be expected, were highly variable, covering several orders of magnitude.

The home and workplace may represent the most important environments for exposure to ETS because of the amount of time individuals spend there. For the five studies reporting residential levels, average nicotine concentrations in homes where smoking occurs ranged from less than 1 $\mu g/m^3$ (Leaderer and Hammond, 1991) to over 14 $\mu g/m^3$ (Muramatsu et al., 1984). For two of the studies (Leaderer and Hammond, 1991; Marbury et al., 1990) nicotine concentrations represent weekly averages. Actual concentrations in the homes during nonsleeping occupancy (i.e., while smoking would be occurring) would be considerably higher than the levels presented in the table (a factor of 3 or more higher). Workplace nicotine also demonstrated a wide range of concentrations, from near zero to over 33 $\mu g/m^3$. In other environments, nicotine concentrations also demonstrated considerable variability. It is important to note that short-term concentrations

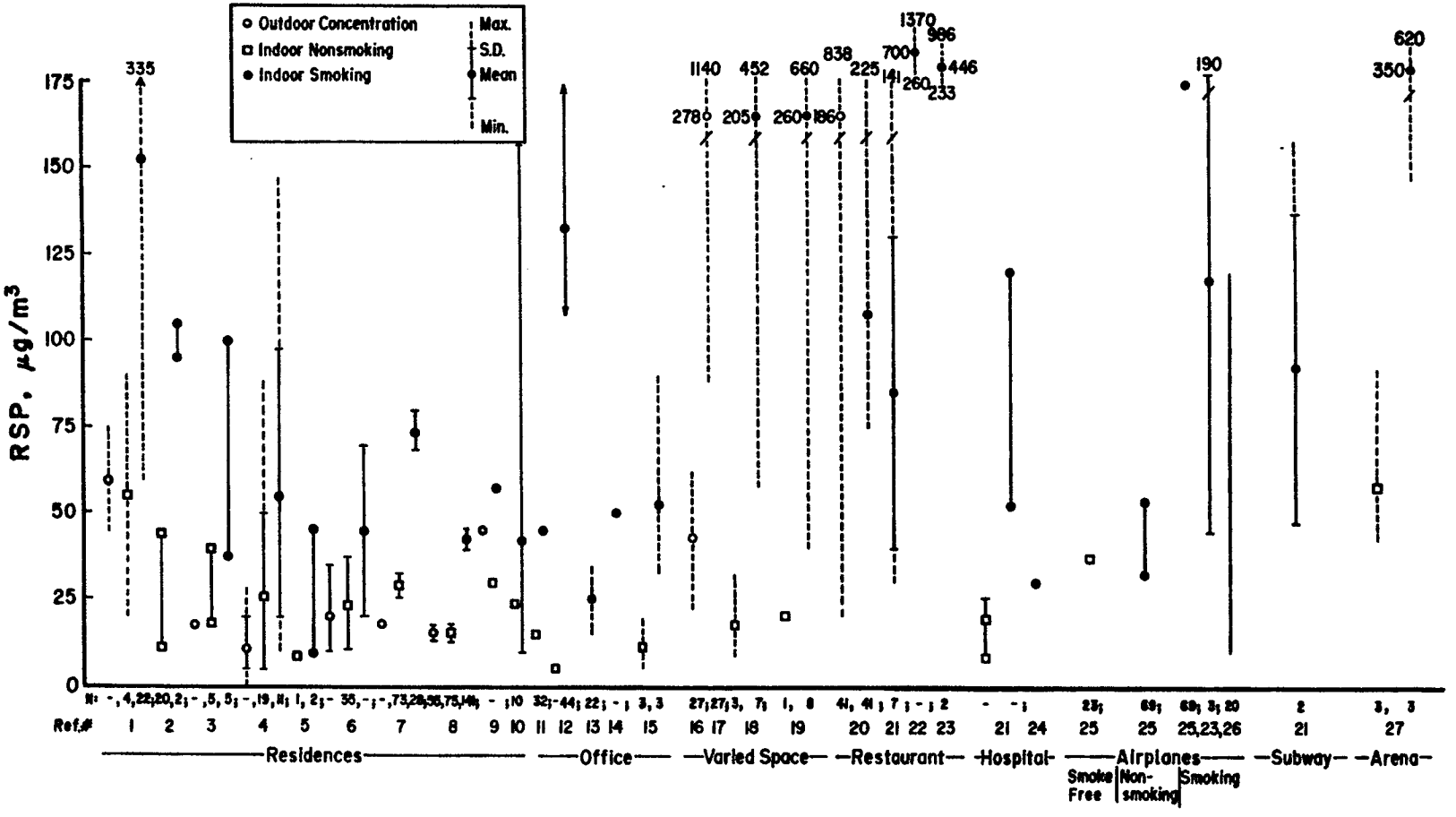


Figure 3-4. Mean, standard deviation, and maximum and minimum nicotine values measured in different indoor environments with smoking occupancy. References from which observations are reported and the number of environments monitored are also given.

REFERENCES FOR FIGURES 3-4 AND 3-5

Figure 3-4

1. Leaderer and Hammond, 1991
2. Mumford et al., 1989
3. Marbury et al., 1990
4. Muramatsu et al., 1984
5. Coultas et al., 1990b
6. Weber and Fischer, 1980
7. Vaughan and Hammond, 1990
8. Leaderer, 1989
9. Miesner et al., 1989
10. Hinds and First, 1975
11. Oldaker et al., 1990
12. Coghlin et al., 1989
13. Badre et al., 1978
14. Higgins, 1987
15. Nagda et al., 1990
16. Eatough et al., 1990
17. Mattson et al., 1989
18. Harmsden and Effenberger, 1957
19. Cano et al., 1970

Figure 3-5

1. Brunekreef and Boleij, 1982
2. Hawthorne et al., 1984
3. Moschandreas, 1981
4. Nitschke et al., 1985
5. Parker et al., 1984
6. Spengler et al., 1981
7. Spengler et al., 1985
8. Leaderer et al., 1990
9. Lebret et al., 1990
10. Coultas et al., 1990b
11. Turk et al., 1987
12. Weber and Fischer, 1980
13. Sterling and Sterling, 1983
14. Nelson et al., 1982
15. Quant et al., 1982
16. Repace and Lowery, 1980
17. Repace and Lowery, 1982
18. Leaderer, 1989
19. First, 1984
20. Oldaker et al., 1990
21. Ishizu, 1980
22. Husgafvel-Pursiainen et al., 1986
23. Eatough et al., 1990
24. Neal et al., 1978
25. Nagda et al., 1990
26. U.S. Department of Transportation, 1971
27. Elliot and Rowe, 1975

(on the order of minutes) are likely to show considerably more variability, resulting in considerably higher short-term peak exposures.

A substantial number of studies examining the impact of tobacco combustion on concentrations of RSP in various indoor environments have been reported. Many of these studies have reported outdoor RSP concentrations and indoor RSP levels without smoking as well as concentrations when smoking occurs. These studies are summarized in Figure 3-5. Outdoor and indoor RSP levels for each of the studies as well as the smoking-associated RSP measurements are shown. The sampling time for the presented data ranged from one minute to over several days. A major portion of the data is for the residential indoor environment. Where smoking is reported, RSP levels are considerably higher than RSP levels outdoors or indoors without smoking. RSP levels associated with smoking, like those for nicotine, demonstrated considerable variability ranging from a few $\mu g/m^3$ to over 1 mg/m^3. Workplace RSP levels associated with smoking occupancy are comparable to residential RSP levels.

In one large residential study, both ETS-associated nicotine and RSP levels were found to be highly correlated ($r = 0.84$; $p < 10^{-5}$) with reported number of cigarettes smoked (Leaderer and Hammond, 1991). This study found that, consistent with chamber data, measured nicotine concentrations predicted the contribution to residential RSP levels from tobacco combustion (Figure 3-6). The data in Figure 3-6 might be used to estimate the RSP levels associated with tobacco combustion from the nicotine levels shown in Figure 3-4. The predictive equation, along with the standard errors, is given in the figure and figure legend. In a study of the impact of smoking on residential levels of RSP and nicotine and of urinary cotinine levels in nonsmoking occupants involving 10 homes, a correlation of 0.54 between residential levels of RSP and nicotine was found (Coultas et al., 1990b).

Indoor levels of nicotine and RSP associated with the combustion of tobacco are a function of several factors related to the generation, dispersal, and removal of ETS in enclosed environments (see Section 3.3.1). Thus, measured levels of these air contaminants indicate a wide range of concentrations (Figures 3-1 and 3-2). Figures 3-7 and 3-8 present a summary of the range of nicotine and ETS-associated particle concentrations measured by type of environment. The figures present the range of average values reported for each study and the minimum and maximum values reported. Only studies reporting sampling times over 4 hours were included in the residential and office summaries in Figures 3-7 and 3-8, because the averaging time is more likely to represent the exposures associated with occupancy time (this included most of the studies for residential spaces shown in Figures 3-4 and 3-5). Since occupancy time in other environments (e.g., restaurants) is likely to be much shorter, averaging times on the order of minutes or greater were considered for the other indoor environments presented in the figures. Indoor particulate

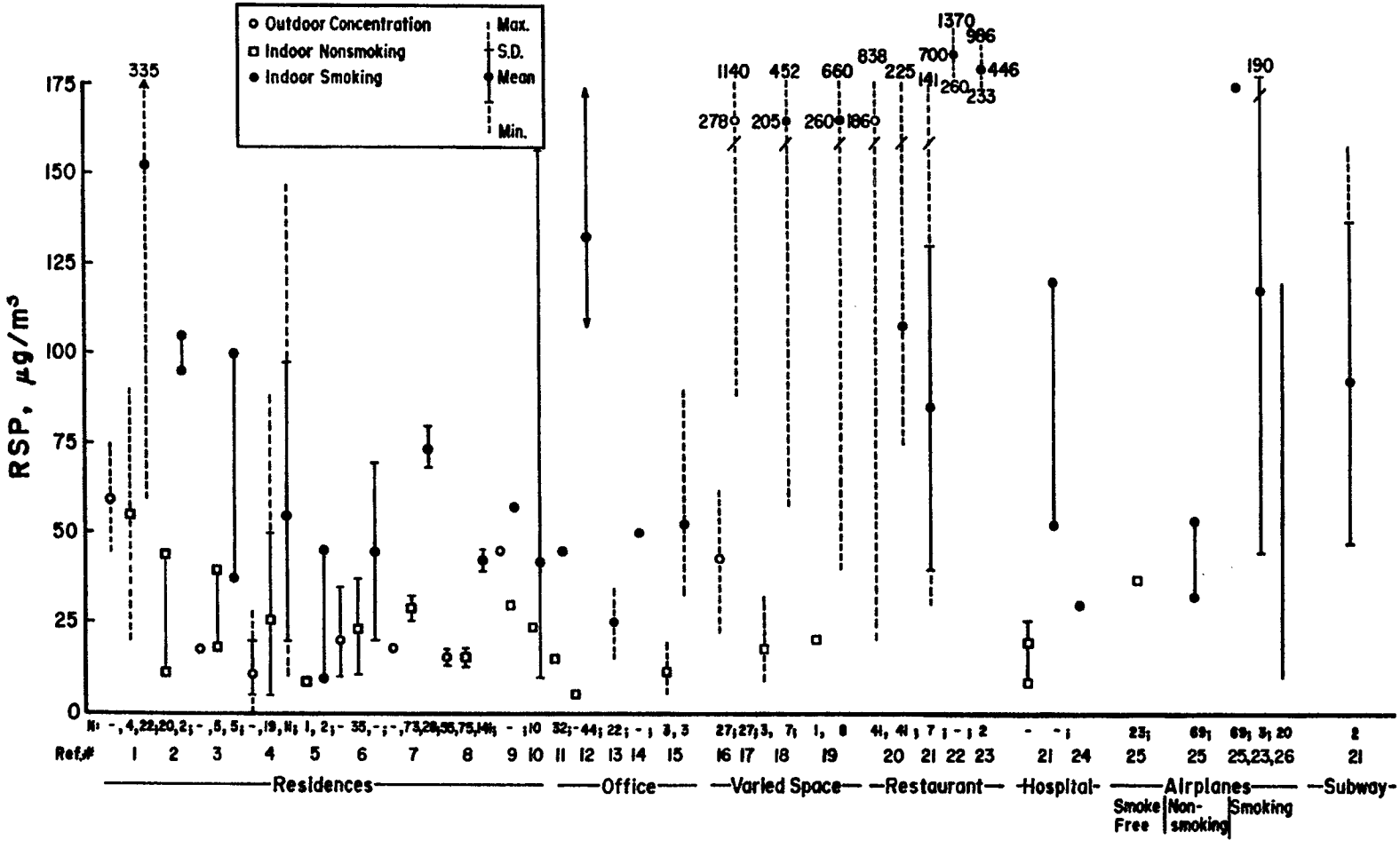


Figure 3-5. Mean, standard deviations, and maximum and minimum concentrations of respirable suspended particle mass (RSP) measured in different indoor environments for smoking and nonsmoking occupancy. Also shown are outdoor concentrations. References from which observations are reported and the number of environments monitored are also given.

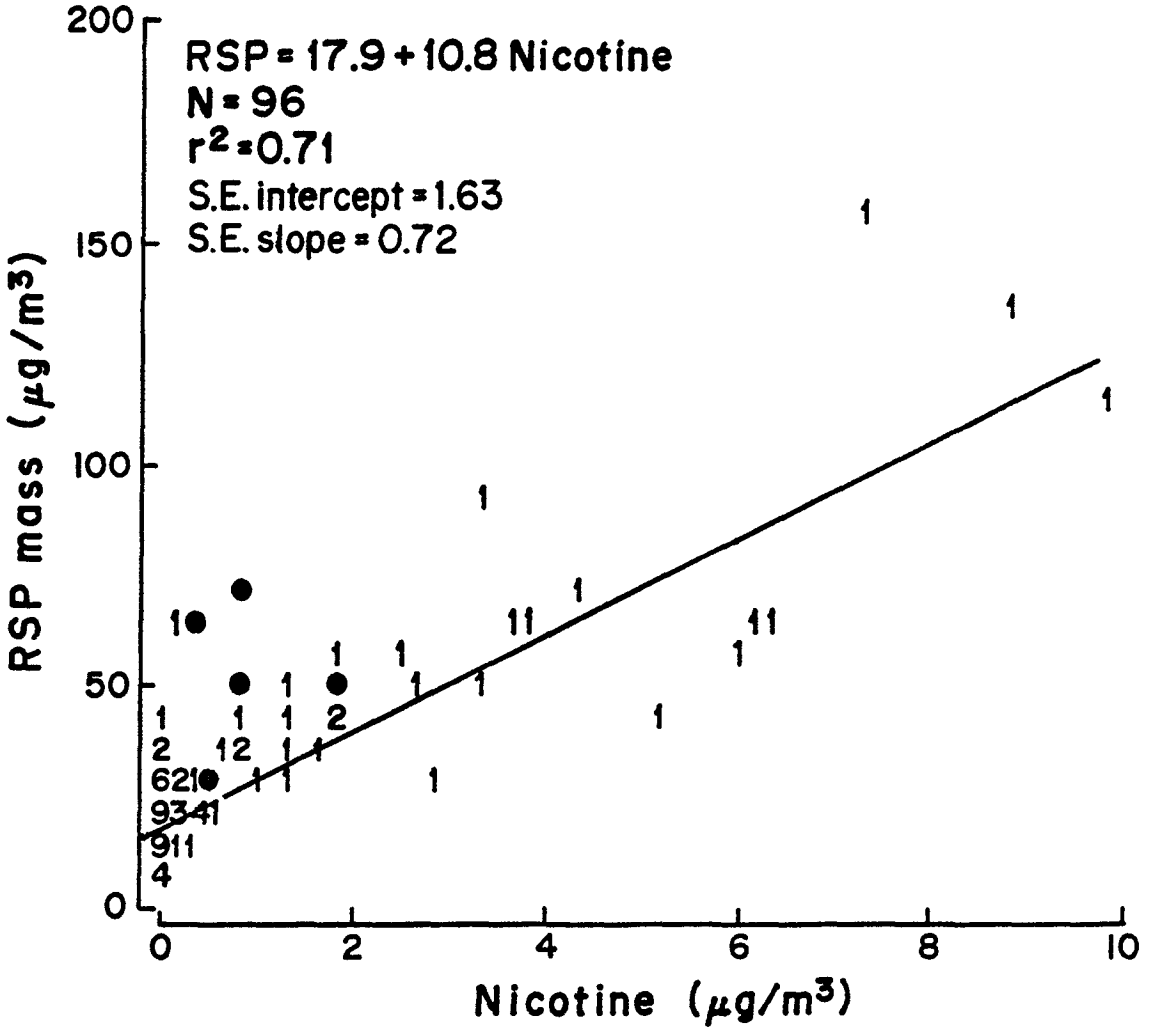


Figure 3-6. Week-long respirable suspended particle mass (RSP) and nicotine measurements in 96 residences with a mixture of sources. Numbers 1-9 refer to the number of observations at the same concentration.

Source: Leaderer and Hammond, 1991.

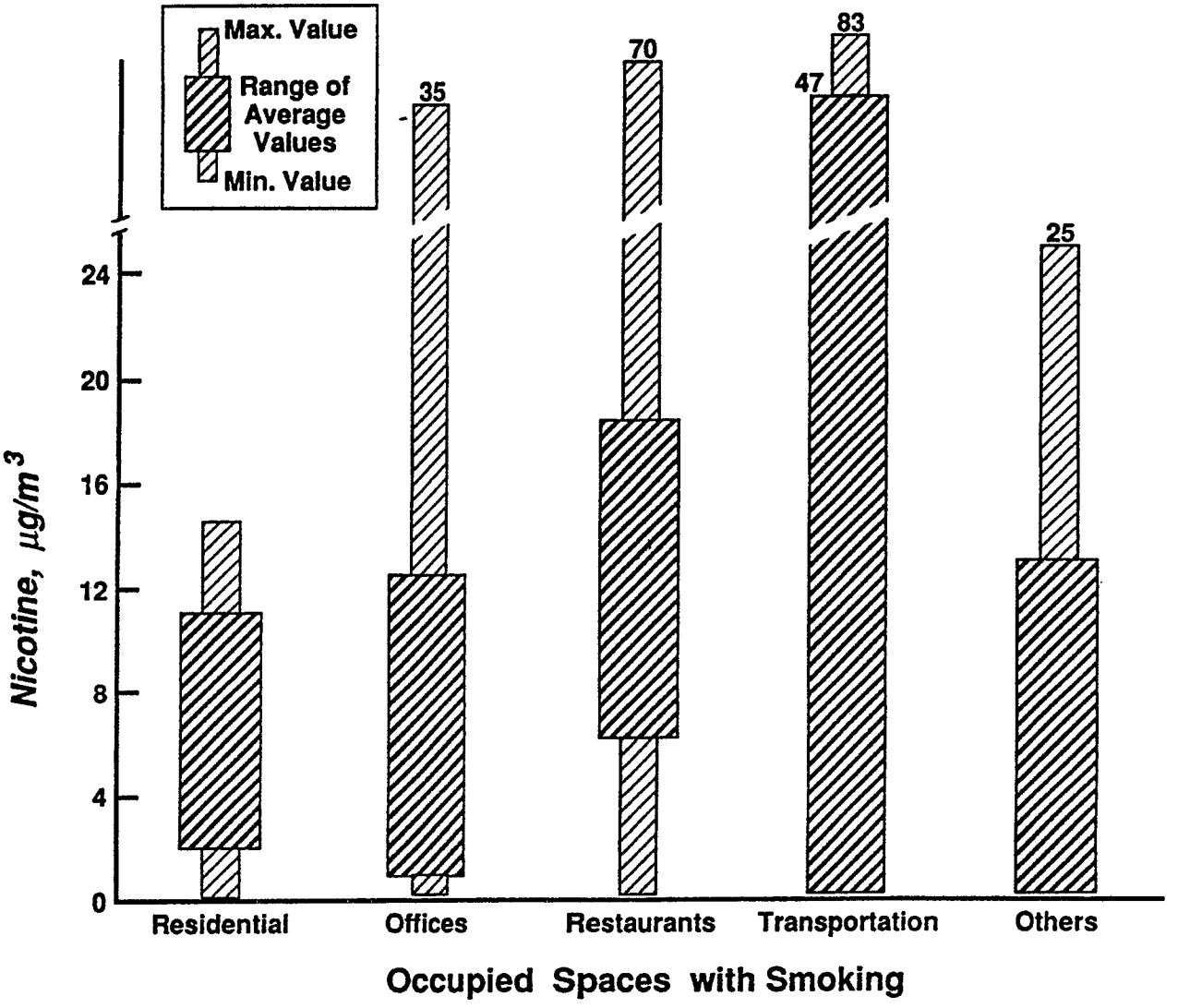


Figure 3-7. Range of average nicotine concentrations and range of maximum and minimum values measured by different indoor environments for smoking occupancy from studies shown in Figure 3-4. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

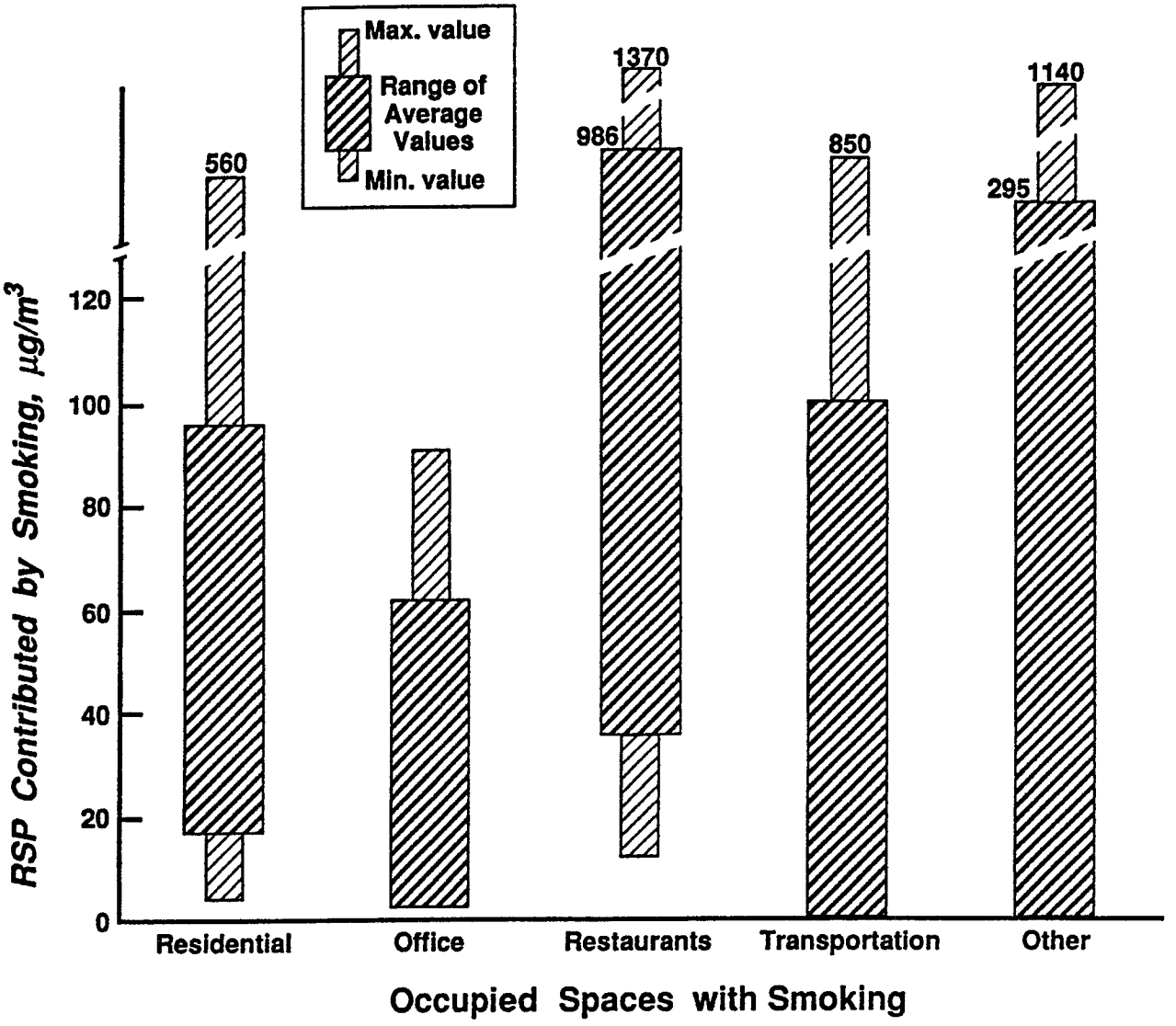


Figure 3-8. Range of average respirable suspended particle mass (RSP) concentrations and range of maximum and minimum values measured by different indoor environments for smoking occupancy from studies shown in Figure 3-5. RSP values represent the contribution to background levels without smoking. Background levels were determined by subtracting reported indoor concentrations without smoking. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

levels associated with smoking occupancy (Figure 3-8) were calculated by subtracting particle levels for nonsmoking occupancy (presented in the studies) from the smoking occupancy levels. Thus, the increase in particle mass concentrations associated with ETS is presented in Figure 3-8. Indoor RSP levels in residences without smokers are typically in the range of 10-25 $\mu g/m^3$, while background office levels are somewhat lower (Figure 3-5).

The summary nicotine data (Figure 3-7) suggest that average nicotine values in residences with smoking occupancy will range from 2 to approximately 10 $\mu g/m^3$, with high values up to 14 $\mu g/m^3$ and low values down to 0.1 $\mu g/m^3$. Offices with smoking occupancy show a range of average nicotine concentrations similar to that of residences, but with considerably higher maximum values. The data from other indoor spaces suggest considerable variability, particularly in the range of maximum values. The cumulative distribution of weekly nicotine measured in one study (Leaderer and Hammond, 1991) for a sample of 96 homes, with the levels for smoking occupancy emphasized, is shown in Figure 3-9.

Particle mass concentrations in smoker-occupied residences show average increases of from 18 to 95 $\mu g/m^3$, while the individual increases can be as high as 560 $\mu g/m^3$ or as low as 5 $\mu g/m^3$ (Figure 3-8). Figure 3-10 (Leaderer and Hammond, 1991) highlights the distribution of weekly RSP concentrations for residences with smoking occupancy. In that study, smoking residences had RSP concentrations approximately 29 $\mu g/m^3$ higher than nonsmoking homes. Concentrations in offices with smoking occupancy will be on average about the same as those in residences. Interestingly, in a large and possibly the most comprehensive study of particle mass concentrations associated with smoking and nonsmoking sites in office buildings (Turk et al., 1987), the geometric mean concentration for RSP in 32 smoking sites was 44 $\mu g/m^3$ while the geometric mean for 35 nonsmoking sites was 15 $\mu g/m^3$. The difference of 29 $\mu g/m^3$ is the same as that found for smoking and nonsmoking residences (Figure 3-10). Restaurants, transportation, and other indoor spaces with smoking occupancy will result in a considerably wider range of average, minimum, and maximum increases in particle concentrations than the residential or office environments.

As noted earlier, indoor air contaminant concentrations are the result of the interaction of a number of factors related to the generation, dispersal, and elimination of the contaminants. Source use is no doubt the most important factor. Few studies have measured contaminant concentrations as a function of the smoking rate in residences or offices, but some data are available. One study estimated an average weekly contribution to residential RSP of 2-5 $\mu g/m^3$ per cigarette (Leaderer et al., 1990), while another study estimated that a pack-a-day smoker would add 20 $\mu g/m^3$ to residential levels (Spengler et al., 1981). Coultas et al. (1990b) estimated

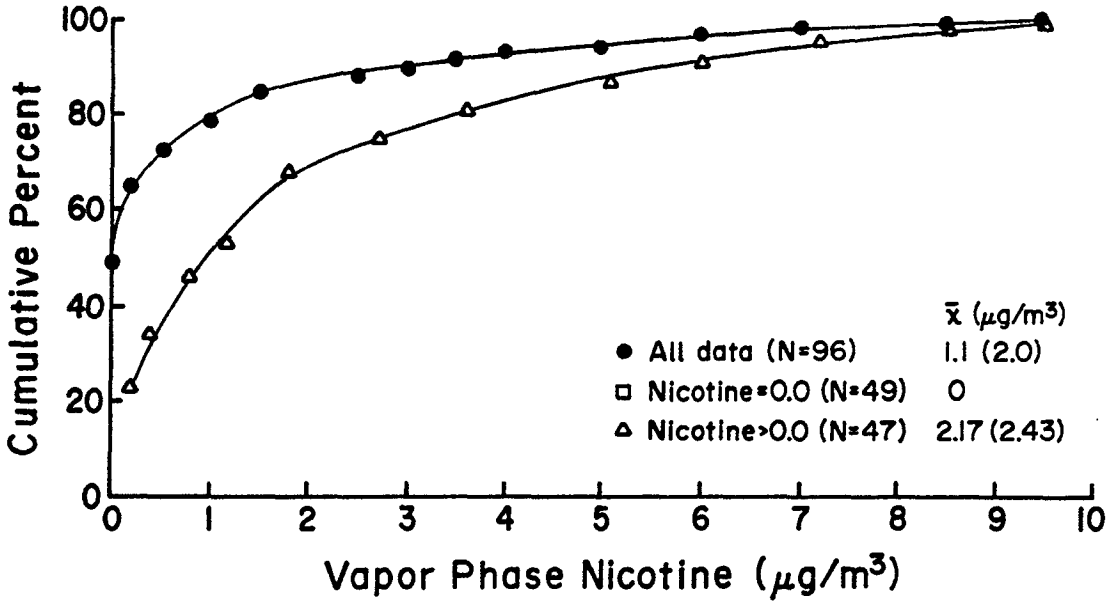


Figure 3-9. Cumulative frequency distribution and arithmetic means of vapor-phase nicotine levels measured over a 1-week period in the main living area in residences in Onondaga and Suffolk Counties in New York State between January and April 1986.

Source: Leaderer and Hammond, 1991.

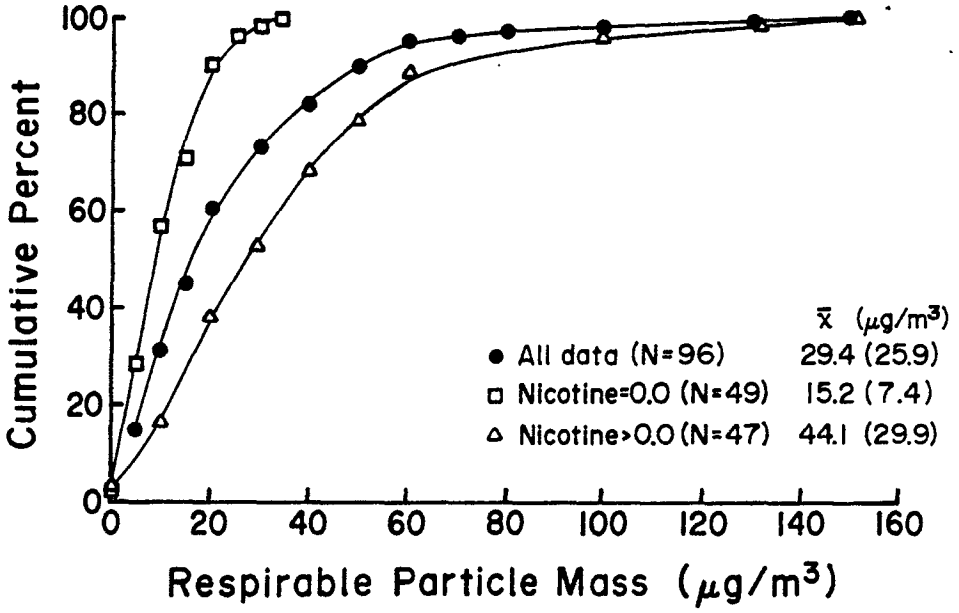


Figure 3-10. Cumulative frequency distribution and arithmetic means of respirable suspended particle mass levels by vapor-phase nicotine levels measured over a 1-week period in the main living area in residences in Onondaga and Suffolk Counties in New York State between January and April 1986.

Source: Leaderer and Hammond, 1991.

that one or more smokers in a home added approximately 17 $\mu g/m^3$ to the residential RSP level. Variations in residential RSP levels as a function of the number of smokers and over a period of several months are demonstrated in Figure 3-11 (Spengler et al., 1981). An association between the reported number of cigarettes and weekly residential nicotine and RSP levels for a sample of 96 homes (Leaderer and Hammond, 1991) is shown in Figure 3-12a and 3-12b. Smoking clearly increases indoor concentrations of both nicotine and particle mass, and residential levels of both nicotine and particle mass increase with increasing levels of smoking. Since nicotine and particle mass are proxies for the complex ETS contaminant mix, other ETS air contaminants, including the toxic and carcinogenic contaminants, should, similarly, be elevated with smoking occupancy. This elevation for selected contaminants is shown in Figure 3-3 and Table 3-3, and for a wider range of contaminants in other publications (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Turk et al., 1987; Brunnemann et al., 1992).

Children have been identified as a particularly sensitive group at health risk from exposure to ETS in the residential indoor environment (NRC, 1986; U.S. DHHS, 1986). One study has measured smoking status of the parents and weekly nicotine concentrations in the activity rooms and bedrooms of 48 children under the age of 2 years (Marbury et al., 1990). The results, shown

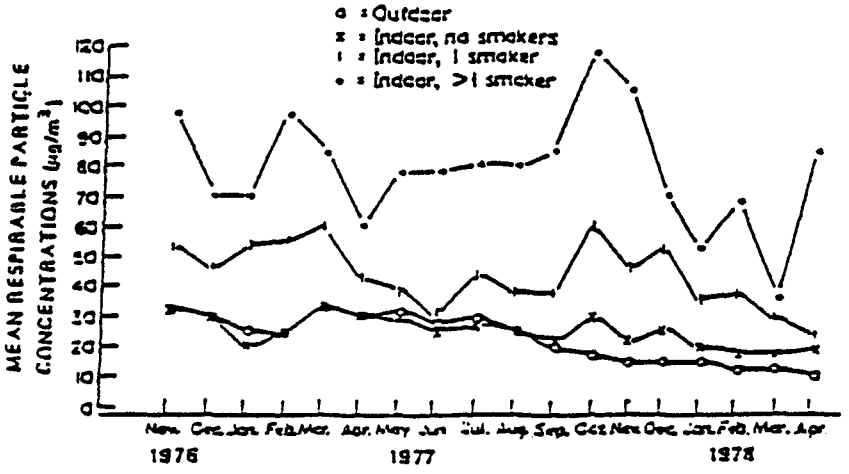


Figure 3-11. Monthly mean respirable suspended particle mass (RSP) concentrations in six U.S. cities.

Source: Spengler et al., 1981.

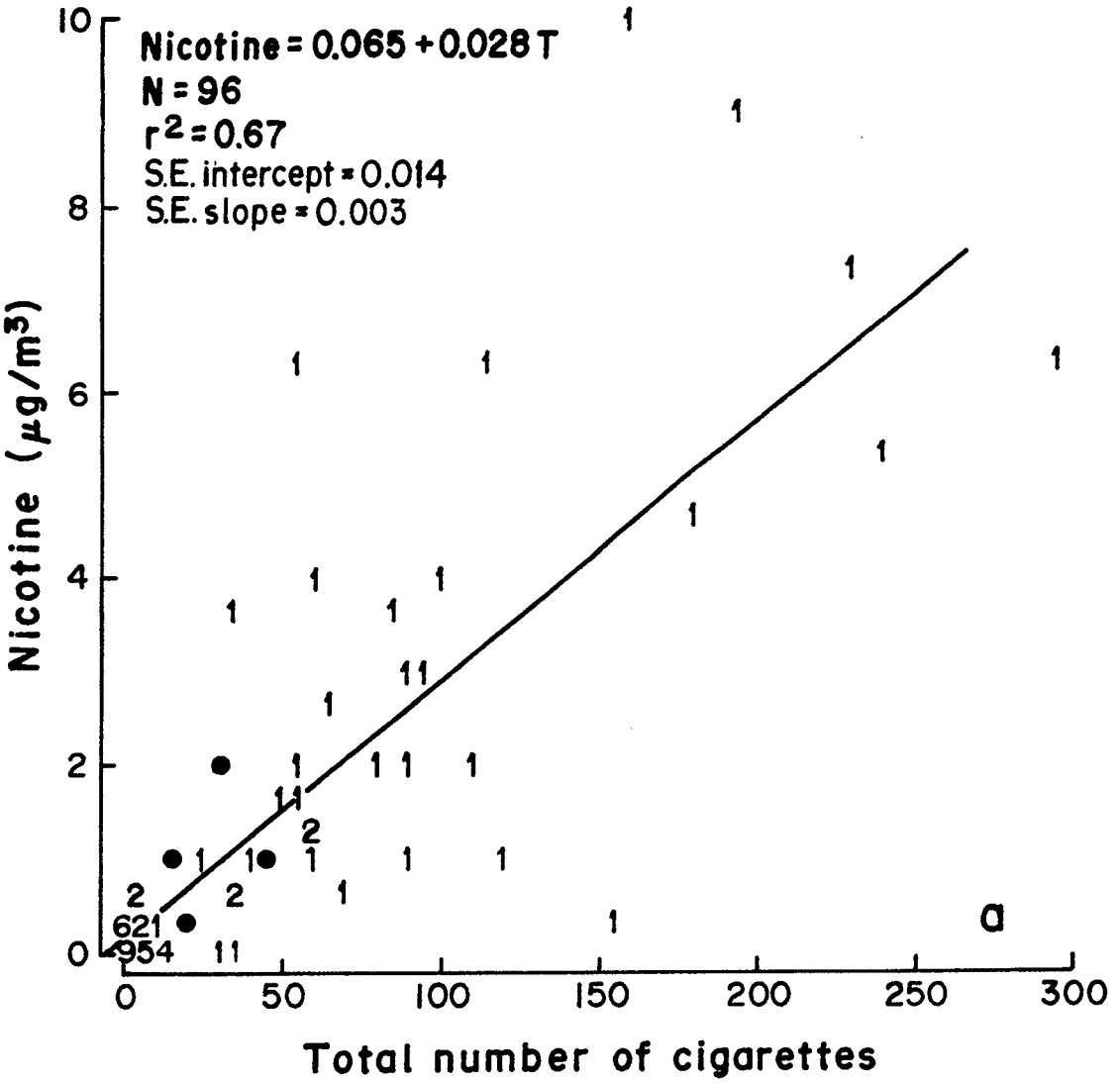


Figure 3-12a. Week-long nicotine concentrations measured in the main living area of 96 residences versus the number of questionnaire-reported cigarettes smoked during the air-sampling period. Numbers 1-9 refer to the number of observations at the same concentrations. Closed circles indicate that cigar or pipe smoking was reported in the houses, with each cigar or pipe smoked set equal to a cigarette. Data from residences in Onondaga and Suffolk Counties in New York State between January and April 1986. For panel (a), the standard errors for the intercept and slope are 0.014 and 0.002, respectively. For panel (b), the standard errors for the intercept and slope are 2.1 and 0.03, respectively.

Source: Leaderer and Hammond, 1991.

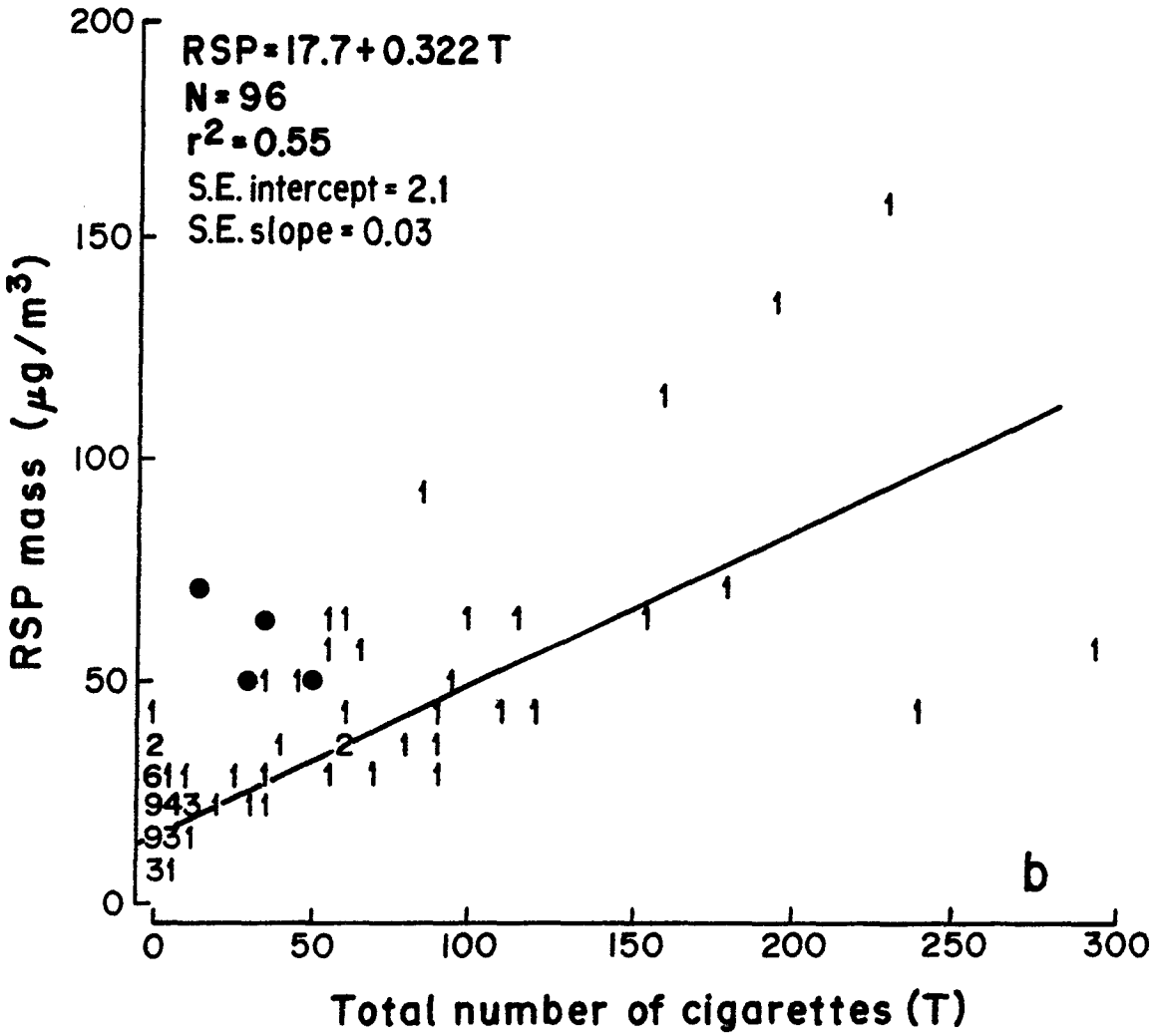


Figure 3-12b. Week-long respirable suspended particle mass (RSP) concentrations measured in the main living area of 96 residences versus the number of questionnaire-reported cigarettes smoked during the air-sampling period. Numbers 1-9 refer to the number of observations at the same concentrations. Closed circles indicate that cigar or pipe smoking was reported in the houses, with each cigar or pipe smoked set equal to a cigarette. Data from residences in Onondaga and Suffolk Counties in New York State between January and April 1986. For panel (a), the standard errors for the intercept and slope are 0.014 and 0.002, respectively. For panel (b), the standard errors for the intercept and slope are 2.1 and 0.03, respectively.

Source: Leaderer and Hammond, 1991.

in Table 3-4, indicate that activity and bedroom concentrations of nicotine in the children's homes increase with the number of cigarettes reported smoked in the home by parents. Concentrations also increased with the number of reported smokers in the household. Correlation coefficients over 0.7 were calculated between nicotine concentrations and number of cigarettes smoked. Exposure of children to ETS is covered in greater detail in Chapter 8.

It is important to note that while measurements of nicotine and ETS-associated RSP are good indicators of the contribution of ETS to air contaminant levels in indoor environments, their measurement does not directly constitute a measure of total exposure. The concentrations measured in all indoor environments have to be combined with time-activity patterns in order to determine average exposure of an individual as the sum of the concentrations in each environment weighted by the time spent in that environment. Both the home and the work environment (those without policies restricting smoking) have highly variable ETS concentrations, with the ranges largely overlapping. Which environment is most important in determining total exposure will vary with individual circumstances (e.g., a person who lives in a nonsmoking home but works in an office with smokers will receive most ETS exposure at work, but for those exposed both at home and at work, the home may be more important because, over the course of a week, more time is generally spent at home).

An additional issue to be considered is how well the general indoor concentrations represent exposures of individuals who may be directly exposed to the SS plume of ETS. Small children, particularly infants, held by smoking parents may receive exposures considerably higher than those predicted from concentrations reported for indoor spaces. Special consideration must be given to these significant subpopulations.

3.3.1.2.2. ***Personal monitors.*** Personal monitoring allows for a direct integrated measure of an individual's exposure. Personal air monitoring employs samplers (worn by individuals) that record the integrated concentration of a contaminant to which individuals are exposed in the course of their normal activity for time periods of several hours to several days. The monitors can be active (employing pumps to collect and concentrate the air contaminant) or passive (working on the principal of diffusion). As with biomarkers, personal monitoring provides an integrated measure of exposure to air contaminants across a number of environments where an individual spends time but does not provide direct information on concentrations of the air contaminant of interest in individual environments or on the level of exposure in each environment unless samples are taken in only one environment or are changed with each change of environment. Supplemental

Table 3-4. Weekly average concentrations of each measure of exposure by parental smoking status in the cross-sectional study, Minnesota, 1989

	Smoking status				
	Non-smokers	Light smokers	Father only	Mother only	Both parents
Number of subjects	23	4	8	6	7
Total cigarettes (no./week)	0.9	28.8	68.6	58.8	227.6
Activity room nicotine ($\mu g/m^3$)	0.15	0.32	2.45	5.50	12.11
Bedroom nicotine ($\mu g/m^3$)	-	0.30	1.21	2.66	5.32

information (air monitoring of spaces, time-activity patterns, etc.) is needed to determine the contribution of each microenvironment to total exposure.

Relatively few studies have measured personal exposures to ETS-associated nicotine and RSP for nonsmoking individuals. The few reported studies of personal exposure to nicotine are summarized in Table 3-5. Personal exposures associated with specific indoor environments are presented. Indoor environments include the nonindustrial workplace, homes, restaurants, public buildings, and transportation-related indoor spaces. Table 3-5 highlights the wide range of indoor environments in which ETS exposures take place and the wide range of personal exposures encountered in those environments. It is important to note, however, that relatively few observations are available and that observations for nonworkplace nicotine exposures are dominated by the Japanese data (Muramatsu), which may not be representative of personal exposures in the United States. Because the data are limited, specific conclusions about the contribution of different indoor environments to personal nicotine exposures associated with passive smoking cannot be drawn. The data do indicate, however, that a wide range of exposures to ETS takes place in a variety of indoor environments where smoking is permitted. The data also indicate that occupational and residential environments are important sources of exposure to ETS because of the levels encountered, which are comparable, and the amount of time individuals spend in them.

Studies of personal exposure to RSP of nonsmoking individuals that have attempted to stratify the collected data by ETS exposure are shown in Table 3-6. Three of the five studies represent exposures integrated over several different microenvironments (residential, public

Table 3-5. Studies measuring personal exposure to airborne nicotine associated with ETS for nonsmokers

Study	Setting	Subject	N	Nicotine, $\mu g/m^3$ X(±SD)	Nicotine, $\mu g/m^3$ Range	Comments
Mattson et al., 1989	Airplane	Attendants	16	4.7 (±4.0)	0.1-10.5	4 attendants on 4 flights
Schenker et al., 1990	Railroad	Clerks	40	6.9		Samples collected over work shifts
Coultas et al., 1990a	Workplace	Nonindustrial	15	20.4 (±20.6)		
Muramatsu et al., 1984	Office	Volunteers	10	21.1		Calculated from data presented
	Laboratory		8	5.8		
	Conference room		5	38.7		
	Home		3	11.2		
	Hospital lobby		1	3.0		
	Hotel lobby		4	11.2		
	Restaurant		15	26.0		
	Transportation		22	21.7		
Muramatsu et al., 1984	Office	Volunteers	3	6.9		Calculated from data presented
	Home		7	7.0		
	Restaurant		15	28.2		
	Car		7	40.0		
	Public transportation		1	11.4		

Table 3-6. Studies measuring personal exposure to particulate matter associated with ETS for nonsmokers

Study	Setting	Number of subjects			Particle mass, $\mu g/m^3$		Particle mass due to ETS
		Total	No ETS exp.	ETS exp.	X (±SD)	Range	$\mu g/m^3$
Spengler et al., 1981	24-hr. day	45			NR	NR	20[a]
Spengler et al., 1985	24-hr. day	101			NR	NR	
			28		NR	NR	28[a]
				73	NR	NR	
Sexton et al., 1984	24-hr. day	48			NR	NR	
			NR		31.7	NR	18.4[1]
				NR	50.1	NR	
Coultas et al., 1990a	Workplace	15			63.9±41.5	4.0-145.8	
			1		4.0		64[2]
				14	68.2±39.5	14.7-145.8	
Schenker et al., 1990	Workplace				86		[3]

[1]Calculated by authors from the regression line.
[2]Calculated from data presented, after the method of Leaderer and Hammond (1991).
[3]Calculated from nicotine exposure, after the method of Leaderer and Hammond (1991).

NR = not reported.

buildings, occupational, etc.), while two studies report exposures for the workplace only. Individuals reporting exposure to ETS have substantially higher integrated exposures to RSP than those reporting no exposure. Passive smoke exposure resulted in increases in personal RSP exposures of 18-64 $\mu g/m^3$. It is difficult to assess the ETS contribution to personal RSP levels for each indoor environment for the 24-hour RSP personal exposures. The contribution of each indoor environment must be substantially higher than the 24-hour averages presented, because exposures presumably did not occur during sleeping hours or in all microenvironments. Table 3-6 demonstrates that the contribution of ETS-related RSP in the work environment to personal exposure is important and variable.

The most extensive study of personal exposure to RSP clearly demonstrates the impact on RSP levels from ETS (Spengler et al., 1985). In this study, outdoor, indoor, and personal 24-hour concentrations of RSP (particle diameter ≤ 3.5 μm) were obtained for a sample of 101 nonsmoking individuals. Of the 101 nonsmokers, 28 persons reported some exposure to ETS in either the home or workplace, while 73 reported no ETS exposure. The cumulative frequency distributions of RSP for the ETS-exposed and non-ETS-exposed individuals and measured outdoor levels are shown in Figure 3-13. Those reporting ETS exposure had mean personal RSP levels 28 $\mu g/m^3$ higher than those reporting no ETS exposure (Table 3-6). A larger variation in RSP concentrations was also seen for those reporting ETS exposure.

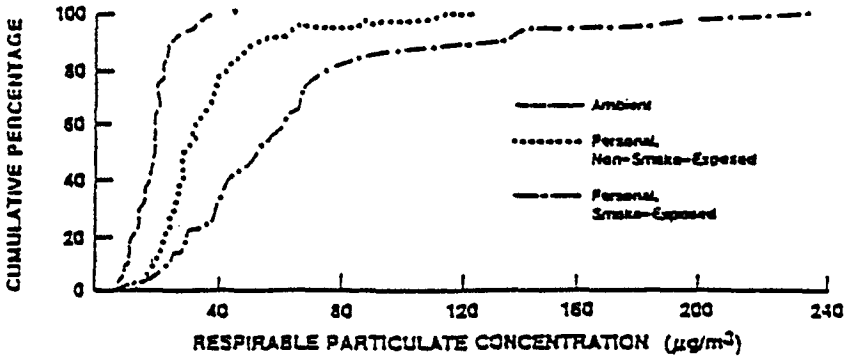


Figure 3-13. Cumulative frequency distribution of respirable suspended particle mass (RSP) concentrations from central site ambient and personal monitoring of smoke-exposed and nonsmoke-exposed individuals.

Source: Spengler et al., 1985.

3.3.2. Biomarkers of ETS Exposure

Biomarkers of exposure are actually measures of dose or uptake and hence indicators that an exposure has taken place. Biomarkers, within the context of assessing exposure to air contaminants, refer to cellular, biochemical, or molecular measures obtained from biological media such as human tissues, cells, or fluids that are indicative of human exposure to air contaminants (NRC and Committee on Biological Markers, 1986; NRC, 1986; Hulka et al., 1990). The relationship between the biomarker and exposure, however, is complex and varies as a function of several factors, including environmental factors and the uptake, distribution, metabolism, and site and mode of action of the compound or compounds of interest.

Ideally, a biomarker of exposure for a specific air contaminant should be chemically specific, have a long half-life in the body, be detectable in trace quantities with high precision, be measurable in samples easily collected by noninvasive techniques, be inexpensive to assay, be either the agent associated with the effects or strongly associated with the agent of interest, and be quantitatively relatable to a prior exposure regimen. Ideal biomarkers for air contaminants, like markers for complex mixtures, do not exist.

Numerous biomarkers have been proposed as indicators for ETS (e.g., thiocyanate, carboxyhemoglobin, nicotine and cotinine, *N*-nitrosoproline, aromatic amines, protein or DNA adducts) (NRC, 1986; U.S. DHHS, 1986). While these biomarkers demonstrate that an exposure has taken place, they may not be directly related to the potential for developing the adverse effect under study (i.e., not the contaminant directly implicated in the effect of interest), they can show considerable variability from individual to individual, and they represent only fairly recent exposure (potentially inadequate for chronic outcomes). Furthermore, some of these markers may not be specific to ETS exposure (e.g., carboxyhemoglobin) while others (e.g., thiocyanate) may not be sensitive enough for ETS exposures.

Nicotine and its metabolite, cotinine, in the saliva, blood, and urine are widely used as biomarkers of active smoking and exposure to ETS and are valuable in determining total or integrated short-term dose to ETS across all environments (NRC, 1986; U.S. DHHS, 1986). Nicotine and cotinine are specific to tobacco and are accurately measured by gas chromatography, radioimmunoassay, or high pressure liquid chromatography in concentrations down to 1 ng/mL. Nicotine has a half-life of about 2 hours in the blood and is metabolized to cotinine and excreted in the urine. The short half-life of nicotine makes it a better indicator of very recent exposures than of integrated exposure.

Cotinine in saliva, blood, and urine is the most widely accepted biomarker for integrated exposure to active smoking or ETS (NRC, 1986; U.S. DHHS, 1986). Cotinine is the major

metabolite of nicotine, is specific to tobacco, and has a longer half-life for elimination from the body. The elimination half-life in smokers is approximately 20 hours (range of 10 to 37 hours), but it is typically longer in nonsmokers with ETS exposure, particularly in children (Figure 3-14) (Collier et al., 1990; Elliot and Rowe, 1975; Goldstein et al., 1987; Etzel et al., 1985; Greenberg et al., 1984). The half-life of cotinine makes it a good indicator of integrated ETS exposure over the previous day or two. Laboratory studies of nonsmokers exposed to acute high levels of ETS over varying times have shown significant uptake of nicotine by the nonsmokers and increases in their cotinine levels (NRC, 1986; U.S. DHHS, 1986; Hoffman et al., 1984; Russell and Feyerabend, 1975).

Cotinine, however, is not an ideal biomarker for ETS, and caution in its use has been suggested (Idle, 1990). Cotinine is only one of the metabolites of nicotine (trans-3'-hydroxycotinine has recently been identified as the major metabolite [Neurath et al., 1988]), and it shows considerable intersubject variability in controlled nicotine exposure studies (Idle, 1990). The assumption that nicotine is specific to tobacco has recently been questioned (Idle, 1990; Sheen, 1988; Castro and Monji, 1986; Davis et al., 1991). Plant sources other than tobacco, primarily from the Solanaceae family, which are common dietary components have been suggested as sources (e.g., eggplant, tomato, and green pepper). It has been suggested that nicotine in food is a natural defense against bacteria, fungi, insects, and animals (Ames, 1983).

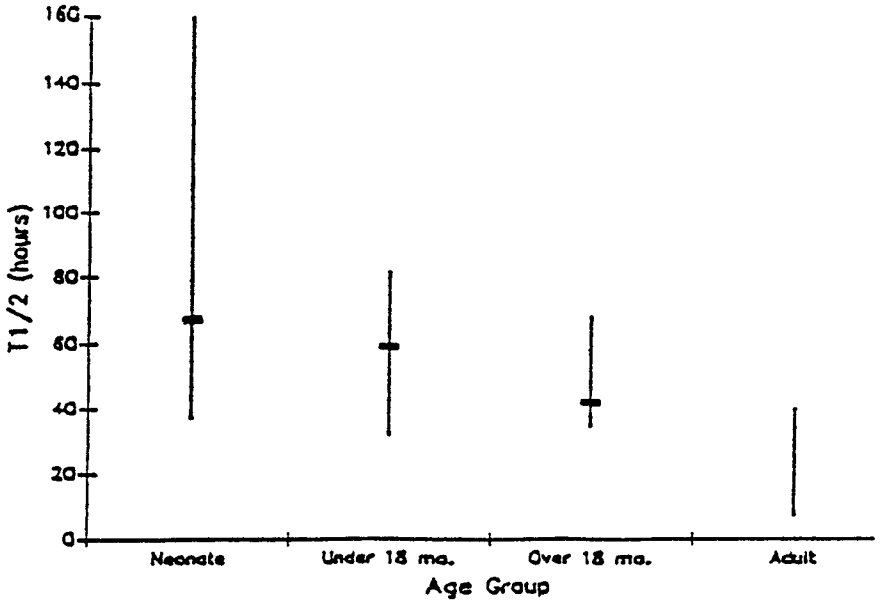


Figure 3-14. Average cotinine $t_{1/2}$ by age groups.

Source: Collier et al., 1990.

Tea has been identified as a particularly high source of dietary nicotine (Sheen, 1988). The impact of dietary nicotine, particularly tea, on cotinine levels of nonsmokers was evaluated in a study of 3,383 men and women 40-59 years of age as part of the Scottish Heart Health Study (Tunstall-Pedoe et al., 1991). The study found a small but inconsistent effect on serum cotinine levels with consumption of 10 or more cups of tea per day with no effect for consumption rates at fewer than 10 cups per day. The authors concluded that "cotinine levels in true nonsmokers reflect far more the nicotine in inhaled ambient tobacco smoke than they do nicotine in tea."

In the most detailed evaluation of nicotine in food, Davis et al. (1991) measured nicotine in a number of teas and foods. They found nicotine levels ranging from less than detectable to 285 ng/g wet weight. The authors calculated that with consuming average quantities of tomatoes, potatoes, cauliflower, and black tea, the average contribution to urinary cotinine levels would be 0.6 ng/mL. High consumption of the foods and tea might result in a maximum urinary cotinine level of 6.2 ng/mL. The average contribution of dietary nicotine intake to urinary cotinine levels might be expected to be below 1 ng/mL and somewhat higher under conditions of high consumption of nicotine-containing foods.

Several population-based studies examined cotinine levels in smokers, nonsmokers reporting passive smoke exposure, and nonsmokers reporting no passive smoke exposure (NRC, 1986; U.S. DHHS, 1986; Greenberg et al., 1984; Wald et al., 1984; Wald and Ritchie, 1984; Jarvis et al., 1985; Coultas et al., 1987; Riboli et al., 1990; Cummings et al., 1990; Tunstall-Pedoe et al., 1991). These studies found that exposure to ETS is highly prevalent even among those living with a nonsmoker (e.g., Cummings et al., 1990). Saliva, serum, and urine cotinine levels in ETS-exposed nonsmokers are generally higher than those in nonsmokers reporting no ETS exposure, and levels of cotinine are considerably higher in smokers than those in nonsmokers passively exposed (e.g., Table 3-7). Cotinine levels in nonsmokers exposed to ETS are approximately 1% of the levels in active smokers. Cotinine levels of nonsmokers have been found to increase with self-reported ETS exposure (e.g., Figures 3-15 and 3-16).

In a 10-country study of ETS exposure of 1,369 nonsmoking women (Riboli et al., 1990), average urinary levels of cotinine/creatinine by country ranged from approximately 2.5 ng/mg for Shanghai to approximately 14 ng/mg for Trieste. Eighty percent of those sampled had a detectable level of cotinine. Statistically significant differences were observed between centers with lowest values observed in Honolulu, Shanghai, and Chandigarh and the highest values in Trieste, Los Angeles, and Athens. This study also found an increase in cotinine/creatinine levels from the group of women reporting no ETS exposure either at home or work (lowest exposure) to the group reporting ETS exposure both at home and at work, the highest exposure group

Table 3-7. Approximate relations of nicotine as the parameter between nonsmokers, passive smokers, and active smokers

Nicotine/cotinine	Nonsmokers without ETS exposure (N = 46)		Nonsmokers with ETS exposure (N = 54)		Active smokers (N = 94)
	Mean value	% of active smokers' value	Mean value	% of active smokers' value	Mean value
Nicotine (ng/mL):					
in plasma	1.0	7.0	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1[1]	0.7	1,750
Cotinine (ng/mL):					
in plasma	0.8	0.3	2.0[1]	0.7	275
in saliva	0.7	0.2	2.5[2]	0.8	310
in urine	1.6	0.1	7.7[2]	0.6	1,390

[1]Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: $p < 0.01$.
[2]Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: $p < 0.001$.

Source: Jarvis, 1987.

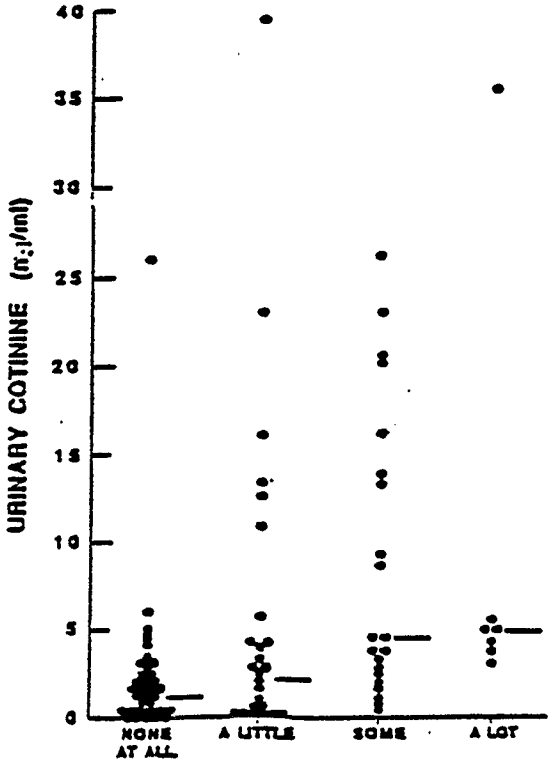


Figure 3-15. Distribution of individual concentrations of urinary cotinine by degree of self-reported exposure to ETS. Horizontal bars indicate median values.

Source: Jarvis and Russell, 1985.

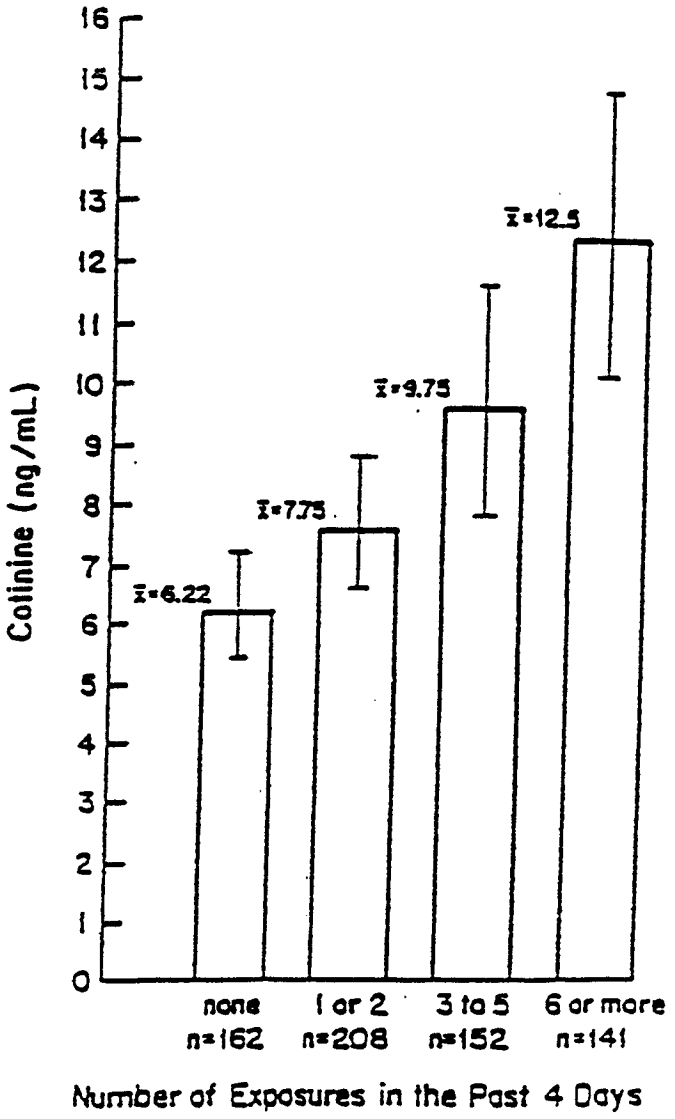


Figure 3-16. Urinary cotinine concentrations by number of reported exposures to tobacco smoke in the past 4 days among 663 nonsmokers, Buffalo, New York, 1986.

Source: Cummings et al., 1990.

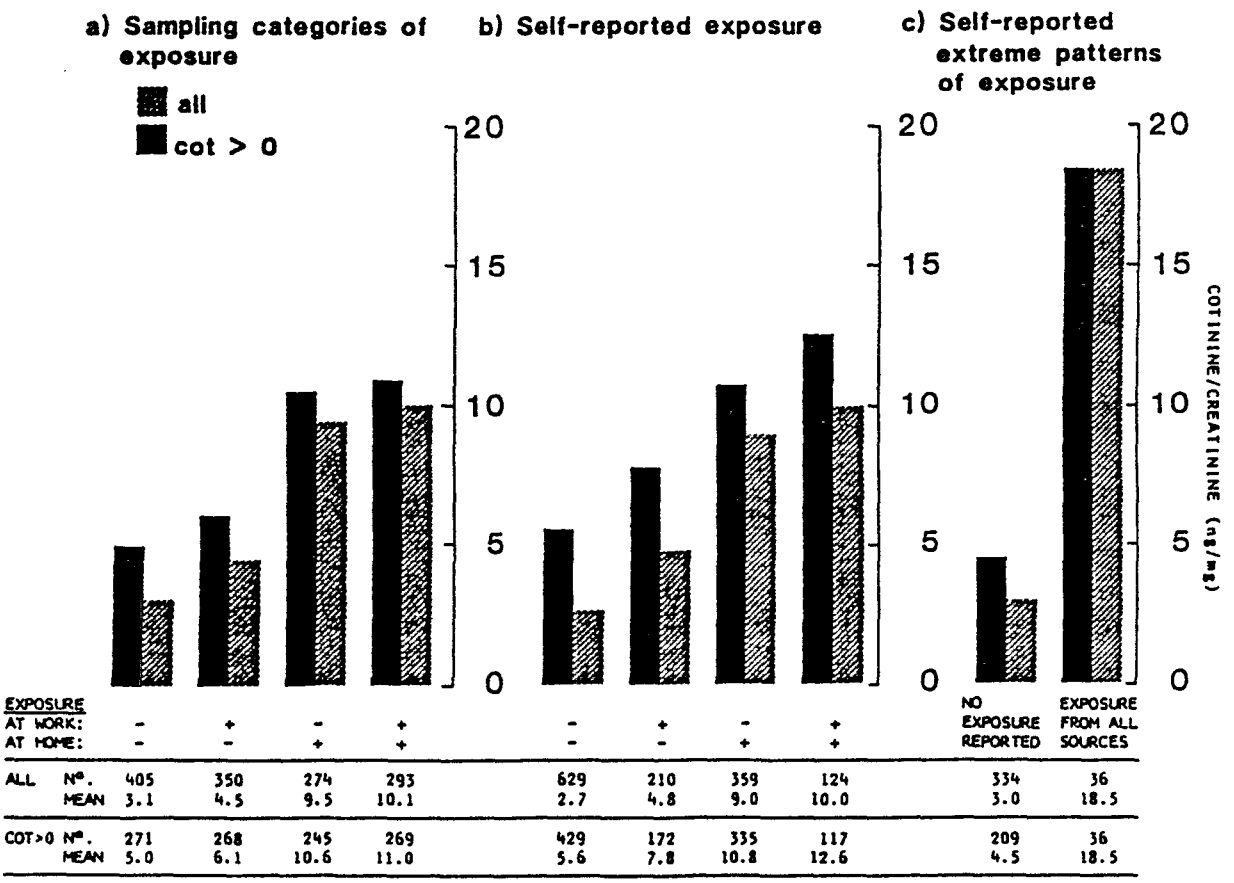
(Figure 3-17). The group of women reporting ETS exposure only at home had cotinine/creatinine levels approximately 60% of those who reported exposure both at home and at work.

Urinary cotinine levels also were found to increase with the number of questionnaire-reported ETS exposures in a group of 663 never-smokers and ex-smokers (Cummings et al., 1990). In that study, 76% of the subjects reported passive smoke exposure in the 4-day period preceding the sampling. Of the total sample, 91% had detectable cotinine levels. Among the 76% reporting ETS exposure, 28% reported exposure at work, 27% at home, 16% in restaurants, 11% at social gatherings, 10% in a car or airplane, and 8% in public buildings. Cotinine levels in this study were also found to vary by month, with the winter months being associated with higher levels and corresponding to higher reported exposures.

Cotinine values in smokers and nonsmokers measured in both the laboratory or field setting show considerable variability due to individual differences in the uptake, distribution, metabolism, and elimination of nicotine. Another issue to be considered in interpreting the field data is that exposure status is determined by respondent self-reporting. This can lead to a misclassification error, which tends to reduce the differences in cotinine levels measured in the ETS-exposed versus non-ETS-exposed groups and to increase the variability in the levels within any exposure category. Within the exposed group, this misclassification error could either increase or decrease the average cotinine levels measured.

It is important to recognize that nicotine and cotinine are actually proxy biomarkers. They may not be the active agents in eliciting the adverse effect under study but merely indicative of the level of passive smoke exposure. Using these measures to estimate cigarette equivalents or determine equivalent active smoking exposure could result in over- or underestimating exposure to individual or classes of compounds that may be more directly related to the health or nuisance effect of concern. Use of different biomarker proxies (e.g., protein adducts) could result in estimates of much larger cigarette equivalent doses.

Nevertheless, nicotine and cotinine levels in ETS-exposed nonsmokers measured in laboratory and field studies have been used to estimate cigarette equivalent exposures and to equate ETS exposures with active smoker exposures (NRC, 1986; U.S. DHHS, 1986; Jarvis, 1989). On an equivalent cigarette basis, an upper-bound estimate of nicotine dose of 2.5 mg/day for a passive smoke exposure has been proposed (Jarvis, 1989). This would translate into the equivalent of about one-fifth of a cigarette per day or about 0.7% of the average smoker's dose of nicotine (cigarette equivalent dose of other toxins or carcinogens would be different--see above). Comparisons of cotinine values in ETS-exposed nonsmokers with those measured in smokers ranged from 0.1% to 2%. One analysis proposed that, on average, nonsmokers' cotinine levels are 0.5%-0.7% of those found in cigarette smokers (Jarvis, 1989). It should be noted that these



EXPOSURE AT WORK:		-	+	-	+	-	+	-	+		
AT HOME:		-	-	+	+	-	-	+	+	NO EXPOSURE REPORTED	EXPOSURE FROM ALL SOURCES
ALL	N°.	405	350	274	293	629	210	359	124	334	36
	MEAN	3.1	4.5	9.5	10.1	2.7	4.8	9.0	10.0	3.0	18.5
COT>0	N°.	271	268	245	269	429	172	335	117	209	36
	MEAN	5.0	6.1	10.6	11.0	5.6	7.8	10.8	12.6	4.5	18.5

Figure 3-17. Average cotinine/creatinine levels for subgroups of nonsmoking women defined by sampling categories of exposure or by self-reporting exposure to ETS from different sources during the 4 days preceding collection of the urine sample.

Source: Riboli et al., 1990.

estimations are based on a number of assumptions that may not hold (e.g., the half-life of nicotine and cotinine in smokers and nonsmokers being the same).

One of the protein adducts used as a biomarker of active and passive smoking is the 4-aminobiphenyl adduct of hemoglobin. One advantage of hemoglobin adducts is that their half-life is quite long and they will persist through the life of a red blood cell, which is approximately 120 days. Therefore, levels of 4-ABP-Hb adducts reflect exposures over the past several weeks, rather than the day or two of exposure integration reflected by cotinine measurements.

Tobacco smoke is the primary environmental source of 4-aminobiphenyl (its use in the dye industry was discontinued decades ago), and smokers have between 5 and 8 times as much 4-ABP-Hb adducts as nonsmokers (Hammond et al., 1990; Perera et al., 1987; Maclure et al., 1989). That nonsmokers appear to have approximately 10-20% the adduct level as smokers may at first appear to be contradictory to the urinary cotinine ratios of about 1%, but in fact both results are quite consistent with our knowledge of the emissions of various contaminants in mainstream and sidestream smoke. Approximately twice as much nicotine is emitted in sidestream as in mainstream smoke, but about 31 times as much 4-ABP is emitted in SS as in MS. Thus, compared to MS, SS is 15 times more enriched in 4-ABP than in nicotine. Similarly, the ratio of biomarkers in those exposed to ETS compared with smokers is roughly 15 times greater for the biomarker 4-ABP-Hb adducts than for the biomarker cotinine, a metabolite of nicotine.

The above discussions indicate that the cigarette equivalent dose of those exposed to ETS varies with the compound, so that a passive smoker may receive 1% as much nicotine as an active smoker but 15% as much 4-ABP. These examples demonstrate the importance of careful interpretation of biomarkers in estimating doses.

3.3.3. Questionnaires for Assessing ETS Exposures

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective and prospective studies of acute and chronic effects. They are the least expensive method to obtain ETS exposure information for large populations. They can be used to provide a simple categorization of ETS exposure, to determine time-activity patterns of individuals (e.g., how much time is spent in environments where smoking occurs), and to acquire information on the factors or properties of the environment affecting ETS concentrations (e.g., number of cigarettes smoked, size of indoor environments, subjective evaluation of level of smokiness). The time-activity pattern information is combined with measured or estimated concentrations of ETS in each environment to provide an estimate of total exposure. Information on the factors affecting ETS concentrations is used to model or predict ETS levels in those environments.

Questionnaires are used most extensively to provide a simple categorization of potential ETS exposure (e.g., do you live with a smoker?, are you exposed to ETS at your place of work?, how many hours a week are you exposed to ETS?) and to obtain information on possible confounders (e.g., occupational history, socioeconomic status). When used simply to determine a dichotomous exposure (ETS-exposed vs. unexposed), any misclassification tends to bias measures of association toward the null. Thus, any effect that may be present will be underestimated or even may not be detectable. If there are more than two exposure categories (e.g, light, medium, or heavy exposure), the intermediate categories of exposure may be biased either away from or toward the null. Misclassification errors may arise from respondents' (1) lack of knowledge, (2) biased recall, (3) memory failure, and (4) intentional alteration of information. Additionally, there are investigator-based sources of misclassification. Errors may arise if semiquantitative levels are incorrectly imputed to answers; e.g., even if house exposures are higher than occupational exposures on average, for any given individual the ranking may well be reversed from that of the average.

In using questionnaires to assess exposure categories to ETS, to determine time-activity patterns, and to acquire information on the factors affecting concentrations, it is important to minimize the uncertainty associated with the estimate and to characterize the direction and magnitude of the error.

Unlike for active smoking assessment, standardized questionnaires for assessing ETS exposures in prospective or retrospective studies of acute or chronic health or nuisance effects do not exist. Lebowitz et al. (1989) reported on an effort to develop a standardized questionnaire to assess ETS exposure in various indoor environments. This questionnaire, however, has not yet been validated. Questionnaires used to assess ETS exposure typically have been developed for specific studies and have not been validated for general use. There is no "gold standard" with which to validate the questionnaires. Various strategies, however, have been used to assess the validity of diverse types of questionnaires used to assess ETS exposure. Efforts to validate questionnaires have used survey data, air monitoring of nicotine in various microenvironments, and nicotine or cotinine in body fluid samples.

A recent study (Leaderer and Hammond, 1991) of 96 homes using a questionnaire to assess residential smoking and a passive nicotine air monitor found that 13% of the residences reporting no smoking had measurable levels of nicotine while 28% of the residences reporting smoking had nondetectable levels of nicotine. A good level of agreement between questionnaire-reported number of cigarettes smoked and residential levels of ETS-related RSP and nicotine was observed in this study (Figures 3-12a and 3-12b).

Studies (Marbury et al., 1990; Coghlin et al., 1989; Coultas et al., 1987, 1990a, 1990b; Riboli et al., 1990; Cummings et al., 1990) comparing various measures of ETS exposure (location of exposure, intensity of exposure, duration of exposure, number of cigarettes smoked, etc.) with cotinine levels measured in physiological fluids generally meet with only moderate success (explained variations on the order of 40% or less). The largest such study (Riboli et al., 1990) was a collaborative effort conducted in 10 countries; correlations in the range of 0.3 to 0.51 ($p < 0.01$) were found between urinary cotinine levels and various measures of exposure derived from questionnaire data. Using cotinine as a biomarker of exposure, studies indicated that a substantial percentage of those reporting no ETS exposure by questionnaire do have measurable exposure. Differences in the uptake, metabolism, and excretion of nicotine among individuals make it difficult to use this measure as a "gold standard" in validating questionnaires. Also, the recent exposure (previous 1-2 days) that is measured by cotinine may differ from usual exposure.

In a study involving 10 homes with 20 nonsmoking and 11 homes with smoking residents, the variability of four markers of ETS exposure (questionnaires, cotinine in saliva and urine, respirable suspended particle mass in air, and nicotine in air) was assessed (Coultas et al., 1990b). Questionnaire-reported exposures explained less than 10% of the variability in air concentrations of suspended particle mass and nicotine, 8% of the variability in urinary cotinine, and 23% of the variability in saliva cotinine. The authors concluded that multiple exposure assessment measurement tools were needed to assess ETS exposure in the home.

In one effort to develop a validated questionnaire (Coghlin et al., 1989), 53 subjects were asked detailed questions about their exposures to ETS, including location of exposures, number of smokers, ventilation characteristics, number of hours exposed, proximity of smokers, and intensity of ETS. They then wore a passive sampler for nicotine for 7 days and recorded the same information regarding each exposure episode in daily diaries. Formulae were developed to score the exposures on both the questionnaire and the diary, and these scores were then correlated to the average nicotine concentrations measured over the 7-day period. Excellent correlation was found ($r^2 = 0.83$ for the questionnaire and 0.90 for the diary). However, the simple questions that have been used most frequently in epidemiologic studies, such as whether a subject lived with a smoker or the number of hours the subject was exposed, were not nearly as well correlated with the measured exposures. These results indicate that reliable questionnaires can be developed, but that those used in most studies in the past will lead to some random misclassification of exposure, and, hence, underestimation of any effect that may be present.

More recently, epidemiologic studies of acute and chronic respiratory effects in children associated with ETS exposure have utilized questionnaires in combination with measurements of cotinine levels in physiologic fluids (Ehrlich et al., 1992; Reese et al., 1992; Etzel et al., 1992).

The studies provide more of a direct link between questionnaire-assessed exposures and objective measures of exposure and disease. Such studies, discussed in Chapter 8, not only provide a means of validating questionnaires but also provide data to establish validation of the risk models used in Chapter 8.

ETS exposures take place across a number of environments, with an individual's total exposure being a function of the amount of time spent in each environment and the concentration in that environment. Questionnaires need to assess exposures across indoor environments. Personal air monitoring provides a method to validate ETS exposure assessment questionnaires and to assess the contribution of each environment to total current exposure.

Personal air monitoring and cotinine measurements in combination with questionnaires have highlighted the importance of obtaining information on spouses' smoking status, smoking at home, smoking at work, smoking in various other indoor environments (social settings, vehicles, public places, etc.), amount of time in environments where smoking occurs, and the intensity of the exposure (Marbury et al., 1990; Coghlin et al., 1989; Coultas et al., 1987, 1990a, 1990b; Riboli et al., 1990; Cummings et al., 1990).

3.4. SUMMARY

ETS is a major source of indoor air contaminants. The ubiquitous nature of ETS in indoor environments indicates that some unintentional inhalation of ETS by nonsmokers is virtually unavoidable. ETS is a dynamic complex mixture of over 4,000 chemicals found in both vapor and particle phases. Efforts to characterize the physical and chemical properties of SS emissions, the principal component of ETS, have found that: (1) MS and SS emissions are qualitatively very similar in their chemical composition, containing many of the same carcinogenic and toxic compounds, (2) several of these compounds, including five known human carcinogens, nine probable human carcinogens, three animal carcinogens, and several toxic agents, are emitted at higher levels in SS than MS smoke (sometimes by an order of magnitude or more); (3) SS emissions of these notable air contaminants demonstrate little variability among brands of cigarettes. The enrichment of several known or suspected carcinogens in SS relative to MS smoke suggests that the SS contaminant mix may be even more carcinogenic than the MS mix, per unit of tobacco burned.

Sidestream emissions, while enriched in several notable air contaminants, are quickly diluted into the environment where ETS exposures take place. Air sampling conducted in a variety of indoor environments has shown that nonsmoker exposure to ETS-related toxic and carcinogenic substances will occur in indoor spaces where there is smoking occupancy. Individuals close to smokers (e.g., an infant in a smoking parent's arms) may be directly exposed

to the plume of SS or exhaled MS, and thus be more heavily exposed than indoor measurements from stationary air monitors might indicate.

Given the complex nature of ETS, it is necessary to identify marker or proxy compounds that when measured will allow for the quantification of exposure to ETS. Vapor phase nicotine and respirable suspended particle mass are two such markers that are suitable indicators of exposure to ETS. Nicotine and RSP have been measured in personal monitoring studies and in studies of a variety of indoor environments. The results of these studies clearly demonstrate that reported exposure to ETS, even under the conditions of low frequency, duration, and magnitude, will result in RSP and nicotine values above background. These studies indicate that ETS exposures take place in a wide range of environments (residences, workplaces, restaurants, airplanes, etc.,) where smoking occurs. Indoor levels of RSP and vapor phase nicotine have been shown to vary in a linear fashion with reported tobacco consumption. Nicotine levels measured indoors have ranged from less than 1 $\mu g/m^3$ to over 500 $\mu g/m^3$, while RSP levels have ranged from less than 5 $\mu g/m^3$ to over 1 mg/m^3. Nicotine exposures greater than 100 $\mu g/m^3$ are exceedingly rare; most environments measured have ranged from less than 0.3 (smoke free) to 30 $\mu g/m^3$; bars and smoking sections of planes may reach 50-75 $\mu g/m^3$. Thus, the normal range of ETS exposures is approximately 100-fold: 0.3 to 30 $\mu g/m^3$ for nicotine and from 5 to 500 $\mu g/m^3$ for RSP.

In residences with smoking occupancy, average daily or weekly nicotine values might typically range from less than 1 to 10 $\mu g/m^3$, varying principally as a function of number of smokers or number of cigarettes smoked. Average daily or weekly residential concentrations of ETS-associated RSP could be expected to increase from 18 to 95 $\mu g/m^3$ (added to background levels) in homes where smoking occurs. Like nicotine, ETS-associated RSP increases with increased smoking. Average levels of nicotine and RSP in offices with smoking occupancy are roughly comparable to those in homes.

Cotinine in saliva, blood, and urine, while not an ideal biomarker, is the most widely accepted biomarker of ETS exposure. Cotinine is an excellent indicator that ETS exposure has taken place. It also establishes the link between exposure and uptake. Studies show that cotinine levels correlate with levels of ETS exposure. The available data also indicate that as many as 80% of nonsmokers are exposed to ETS and that there is variability in average exposure levels among nonsmokers in different geographical regions.

Although average cotinine levels are a useful indicator of relative doses of ETS among different groups of nonsmokers, the ratio of cotinine levels in nonsmokers versus smokers may not be indicative of the exposure ratio for the active agents in ETS and MS responsible for the adverse effects. For example, while comparisons of cotinine levels in smokers and nonsmokers have led to

estimates that ETS-exposed nonsmokers receive from 0.1 to 0.7% of the dose of nicotine of an average smoker, ETS-exposed nonsmokers may receive 10-20% of the dose of 4-ABP that smokers inhale.

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective and prospective studies of acute and chronic effects. They have been used not only to establish simple categories of ETS exposure but also to obtain information on activity patterns of exposed individuals and on environmental factors affecting concentrations in different indoor environments. No standardized or validated questionnaires have yet been developed for assessing ETS exposure. A number of studies have compared questionnaire responses to measured air concentrations of nicotine and RSP and to cotinine levels. These efforts have indicated that a significant percentage of individuals reporting no exposure had actually been exposed. In general, questionnaires had moderate success in assessing exposure status and level of exposure. Misclassification errors must be addressed when using questionnaires to assess ETS exposure.

In summary, ETS represents an important source of toxic and carcinogenic indoor air contaminants. The available data suggest that exposure to ETS is widespread, with a wide range of exposure levels.

4. HAZARD IDENTIFICATION I: LUNG CANCER IN ACTIVE SMOKERS, LONG-TERM ANIMAL BIOASSAYS, AND GENOTOXICITY STUDIES

4.1. INTRODUCTION

Numerous epidemiologic studies have conclusively established that the tobacco smoke inhaled from active smoking is a human lung carcinogen (U.S. DHHS, 1982; IARC, 1986). A clear dose-response relationship exists between lung cancer and amount of exposure, without any evidence of a threshold level. It is, therefore, reasonable to theorize that exposure to environmental tobacco smoke (ETS) might also increase the risk of lung cancer in both smokers and nonsmokers.

As documented in the previous chapter, the chemical compositions of mainstream smoke (MS) and ETS are qualitatively similar, and both contain numerous known or suspected human carcinogens. In fact, ETS contains essentially all of the same carcinogens identified in MS, and many of these appear in greater amounts in sidestream smoke (SS), the primary component of ETS, than in MS, per unit tobacco burned (Table 3-1). In addition, both MS and SS have been shown to be carcinogenic in animal bioassays (Wynder and Hoffman, 1967; Grimmer et al., 1988), and MS, SS, and ETS have all been found to be genotoxic in in vitro systems (IARC, 1986). Furthermore, as the previous chapter also describes, exposure assessments of indoor air and measurements of nicotine and cotinine levels in nonsmokers confirm that passive smokers are exposed to and absorb appreciable amounts of ETS that might result in elevated lung cancer risk.

This chapter reviews the major evidence for the lung carcinogenicity of tobacco smoke derived from human studies of active smoking and the key supporting evidence from animal bioassays and in vitro experiments. The evidence from the few animal and mutagenicity studies pertaining specifically to ETS is also presented. The majority of this information has already been well documented by the U.S. Department of Health and Human Services (U.S. DHHS) (1982) and the International Agency for Research on Cancer (IARC) (1986). The current discussion mainly extracts and summarizes some of the important issues and principal studies described in those comprehensive reports.

In view of the abundant and consistent human evidence establishing the carcinogenic potential of active smoking to the lung, the bulk of this chapter focuses on the human data. Although EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a) suggest an extensive review of all evidence pertaining to carcinogenicity, we believe that the large quantity of human cancer studies on both MS and ETS provide the most appropriate database from which to evaluate the lung cancer potential of ETS. Thus, the animal evidence and genotoxicity results are given only limited attention here. Similarly, a discussion of the mutagenicity data for individual smoke

components would be superfluous in the context of the overwhelming evidence from other, more pertinent sources and is not included. Extensive reviews of these data can be found in the U.S. DHHS (1982) and IARC (1986) publications. Claxton et al. (1989) provide an assessment of the genotoxicity of various ETS constituents.

4.2. LUNG CANCER IN ACTIVE SMOKERS

Studies of active smoking in human populations from many countries provide direct and incontrovertible evidence for a dose-related, causal association between cigarette smoking and lung cancer. This evidence includes time trends in lung cancer mortality rates associated with increasing cigarette consumption, high relative risks for lung cancer mortality in smokers of both sexes observed consistently in numerous independent retrospective and prospective studies, and dose-response relationships demonstrated with respect to smoking intensity and duration and for all four major histological types of lung cancer.

4.2.1. Time Trends

While the overall cancer death rate in the United States has been fairly stable since 1950, the lung cancer death rate has increased drastically for both males and females (Figures 4-1 and 4-2). Age-adjusted lung cancer mortality rates in men have increased from 11 per 100,000 in 1940 to 73 per 100,000 in 1982, leveling slightly to 74 per 100,000 in 1987 (Garfinkel and Silverberg, 1991). In women, lung cancer mortality rates have risen from 6 per 100,000 in the early 1960's to 28 per 100,000 in 1987 (Garfinkel and Silverberg, 1991).

The striking time trends and sex differences seen in lung cancer mortality rates correlate with historical smoking patterns. Increases in lung cancer death rates parallel increases in cigarette consumption with a roughly 20-year lag time, accounting for the latency period for the development of smoking-induced lung cancer. Males started smoking cigarettes in large numbers during the years around World War I, whereas females did not begin smoking in appreciable numbers until World War II. Cigarette consumption per capita (based on the total population age 18 and older) in the United States rose from 1,085 in 1925 to a high of 4,148 in 1973. In the past two decades, cigarette consumption has decreased to 2,888 in 1989 (Garfinkel and Silverberg, 1991). This decline correlates with the leveling off of lung cancer mortality rates in recent years.

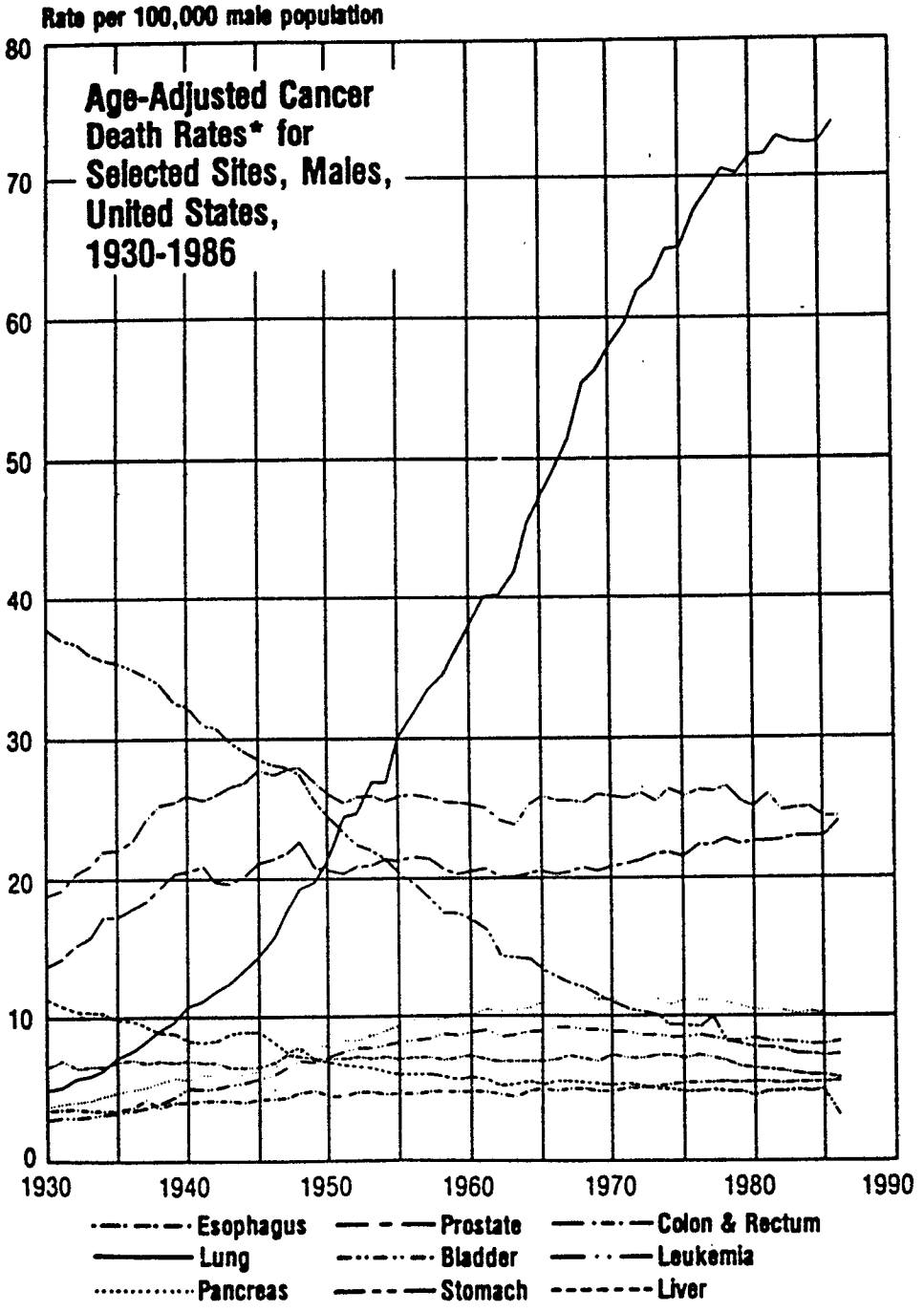


Figure 4-1. Age-adjusted cancer death rates* for selected sites, males, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

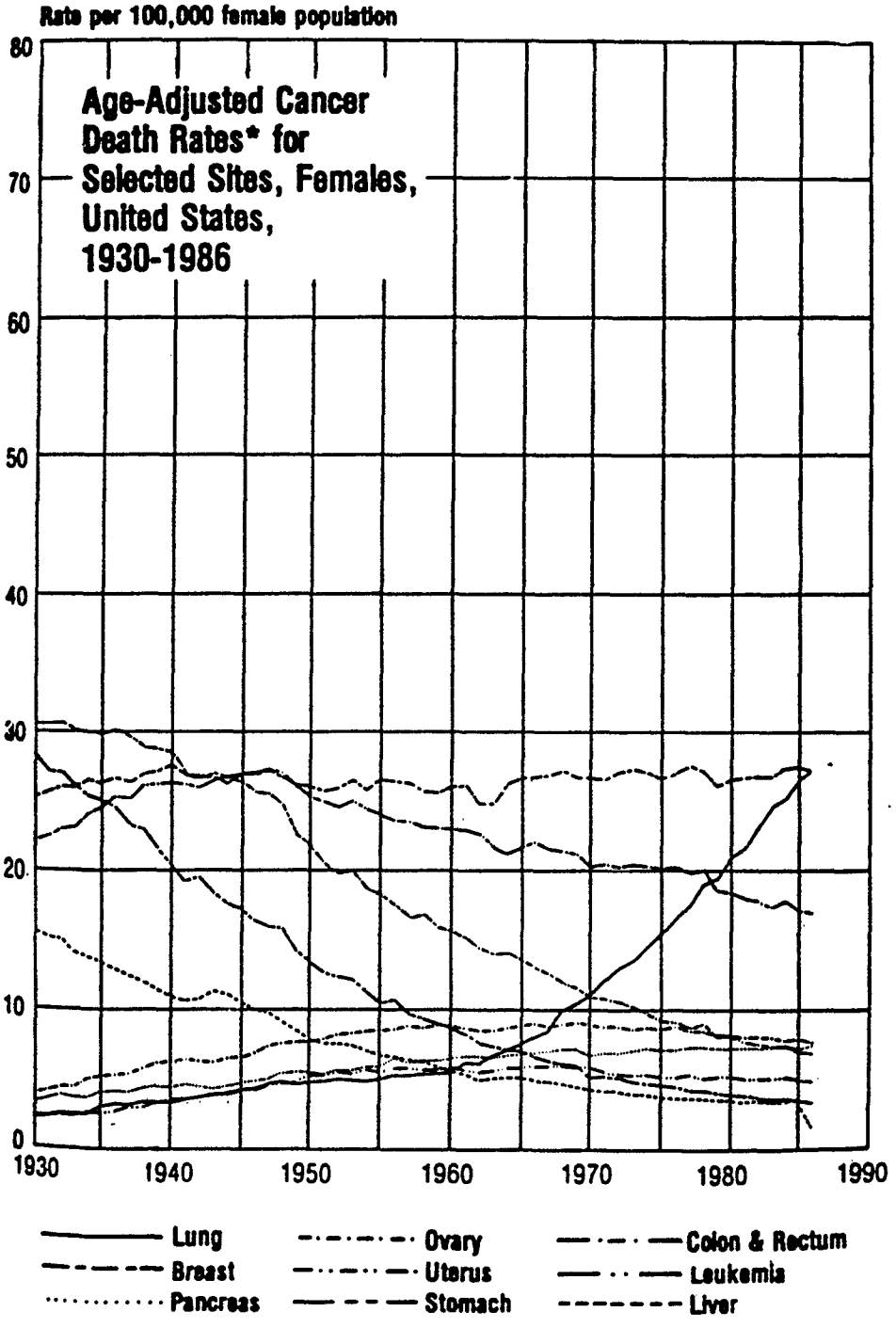


Figure 4-2. Age-adjusted cancer death rates* for selected sites, females, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

4.2.2. Dose-Response Relationships

More than 50 independent retrospective studies have consistently found a dose-related association between smoking and lung cancer (U.S. DHHS, 1982). Eight major prospective studies from five countries corroborate this association:

- American Cancer Society (ACS) Nine-State Study (white males) (Hammond and Horn, 1958a,b)
- Canadian War Veterans Study (Best et al., 1961; Lossing et al., 1966)
- British Doctors Study (Doll and Hill, 1964a,b; Doll and Peto, 1976; Doll et al., 1980)
- American Cancer Society 25-State Study (Hammond, 1966; Hammond and Seidman, 1980)
- U.S. Veterans Study (Kahn, 1966; Rogot and Murray, 1980)
- California Labor Union Study (Weir and Dunn, 1970)
- Swedish Study (sample of census population) (Cederlöf et al., 1975)
- Japanese Study (total population of 29 health districts) (Hirayama, 1967, 1975a,b, 1977, 1978, 1982, 1985).

Details of the designs of these studies are summarized in Table 4-1. These eight studies together represent more than 17 million person-years and more than 330,000 deaths. Lung cancer mortality ratios from the prospective studies are presented in Table 4-2. Combining the data from the prospective studies results in a lung cancer mortality ratio of about 10 for male cigarette smokers compared with nonsmokers. (Note that these lung cancer mortality ratios underestimate the relative risk of lung cancer to smokers compared with a non-tobacco-smoke-related background risk to nonsmokers [see Chapter 6], given the causal association between ETS exposure and lung cancer in nonsmokers documented in this report.)

This strong association between smoking and lung cancer is further enhanced by very strong and consistent dose-response relationships. A gradient of increasing risk for lung cancer mortality with increasing numbers of cigarettes smoked per day was established in every one of the prospective studies (Table 4-3). Lung cancer mortality ratios for male smokers who smoked more than 20 cigarettes daily were generally 15 to 25 times greater than those for nonsmokers. Marked increases in lung cancer mortality ratios were also seen in all the lowest dose categories. Males who smoked fewer than 10 cigarettes per day had lung cancer mortality ratios 3 to 10 times greater than those for nonsmokers. There is no evidence of a threshold level for the development of smoking-induced lung cancer in any of the studies.

Dose-response relationships with respect to the duration of smoking also have been well established. From the British male physicians study, Peto and Doll (1984) calculated that the

Table 4-1. Main characteristics of major cohort studies on the relationship between smoking and cancer

Study	Year of enrollment	Sample size; initial samples; in brackets, population for followup	Source of information on smoking (proportion of respondents)	Duration of followup and no. of deaths	Completeness of followup for mortality
ACS 9-state study	1952	204,547 men [187,783]	Self-administered questionnaire	44 months 11,870 deaths	98.9%
Canadian veterans study	1955-1956	207,397 subjects (aged 30+) [92,000]	Self-administered questionnaire (57% respondents)	6 years 9,491 deaths in men; 1,794 deaths in women	NA
British doctors study	1951	34,440 men (aged 20+)	Self-administered questionnaire (69% respondents)	20 years 10,072 deaths	99.7%
		6,194 women (aged 20+)	Self-administered questionnaire (60% respondents)	22 years 1,094 deaths	99%
ACS 25-state study	1959-1960	1,078,894 subjects, first followup: 440,558 men, 562,671 women (aged 35-84); second followup: 358,422 men, 483,519 women	Self-administered questionnaire	4.5 + 5 years 26,448 deaths in men; 16,773 deaths in women	97.4% in women 97.9% in men in first followup
U.S. veterans study	1954	293,958 men (aged 31-84) [248,046]	Self-administered questionnaire (85% respondents)	16 years 107,563 deaths	Almost 100% ascertainment of vital status; 97.6% of death certificates retrieved
California study	1954-1957	68,153 men (aged 35-64)	Self-administered questionnaire	5-8 years 4,706 deaths	NA

(continued on the following page)

Table 4-1. (continued)

Study	Year of enrollment	Sample size; initial samples; in brackets, population for followup	Source of information on smoking (proportion of respondents)	Duration of followup and no. of deaths	Completeness of followup for mortality
Swedish study	1963	27,342 men, 27,732 women (aged 18-69)	Self-administered questionnaire (89% respondents)	10 years 5,655 deaths (2,968 autopsies)	NA
Japanese study	1965	122,261 men, 142,857 women (aged 40+)	Interview (95% of population in area)	16 years 51,422 deaths	Total

NA = not available.

Source: IARC, 1986.

Table 4-2. Lung cancer mortality ratios--prospective studies

Population	Size	Number of deaths	Nonsmokers	Cigarette smokers
British doctors study	34,000 males 6,194 females	441 27	1.00 1.00	14.0 5.0
Swedish study	27,000 males 28,000 females	55 8	1.00 1.00	7.0 4.5
Japanese study	122,000 males 143,000 females	940 304	1.00 1.00	3.76 2.03
ACS 25-state study	358,000 males 483,000 females	2,018 439	1.00 1.00	8.53 3.58
U.S. veterans study	290,000 males	3,126	1.00	11.28
Canadian veterans study	78,000 males	331	1.00	14.2
ACS 9-state study	188,000 males	448	1.00	10.73
California males in 9 occupations	68,000 males	368	1.00	7.61

Source: U.S. DHHS, 1982.

Table 4-3. Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day--prospective studies

	Men		Women	
Population	Cigarettes smoked per day	Mortality ratios	Cigarettes smoked per day	Mortality ratios
ACS 25-state study	Nonsmoker	1.00	Nonsmoker	1.00
	1-9	4.62	1-9	1.30
	10-19	8.62	10-19	2.40
	20-39	14.69	20-39	4.90
	40+	18.71	40+	7.50
British doctors study	Nonsmoker	1.00	Nonsmoker	1.00
	1-14	7.80	1-14	1.28
	15-24	12.70	15-24	6.41
	25+	25.10	25+	29.71
Swedish study	Nonsmoker	1.00	Nonsmoker	1.00
	1-7	2.30	1-7	1.80
	8-15	8.80	8-15	11.30
	16+	13.70	16+	--
Japanese study (all ages)	Nonsmoker	1.00	Nonsmoker	1.00
	1-19	3.49	<20	1.90
	20-39	5.69	20-29	4.20
	40+	6.45		
U.S. veterans study	Nonsmoker	1.00		
	1-9	3.89		
	10-20	9.63		
	21-39	16.70		
	≥40	23.70		
ACS 9-state study	Nonsmoker	1.00		
	1-9	8.00		
	10-20	10.50		
	20+	23.40		
Canadian veterans study	Nonsmoker	1.00		
	1-9	9.50		
	10-20	15.80		
	20+	17.30		
California males in 9 occupations	Nonsmoker	1.00		
	about ½ pk	3.72		
	about 1 pk	9.05		
	about 1½ pk	9.56		

Source: U.S. DHHS, 1982.

excess annual incidence rates of lung cancer after 45, 30, and 15 years of cigarette smoking were in the approximate ratio of 100:20:1 to each other. The California and Swedish studies also demonstrated an increasing risk of lung cancer in men with longer smoking duration (Table 4-4).

Four of the prospective studies examined lung cancer mortality in males by age at initiation of smoking and found increasing risk with younger age (Table 4-5). Some of the studies also investigated smoking cessation in men and observed a decrease in lung cancer risk with increasing number of years since quitting smoking (Table 4-6). The Cancer Prevention Study II, a study of 1,200,000 people in all 50 states, reveals a similar trend for women who quit smoking (Figure 4-3). The occurrence of higher lung cancer mortality ratios in the groups with only a few years since cessation as compared with current smokers (Table 4-6 and Figure 4-3) is attributable to the inclusion of recent ex-smokers who were forced to stop smoking because they already had smoking-related symptoms or illness (U.S. DHHS, 1990a). The increased lung cancer risks seen in people who started smoking at a younger age and the decreased risks seen with time since smoking cessation suggest both initiation and promotion capabilities of tobacco smoke components.

Additional dose-response relationships have been derived from consideration of the types of tobacco products used. Pipe and cigar smokers, who inhale less deeply than cigarette smokers, have lower risks of lung cancer than cigarette smokers (Table 4-7). Furthermore, the American Cancer Society 25-state study found decreased risks for lung cancer in males and females who smoked cigarettes with lower tar and nicotine content compared with those who smoked cigarettes with higher tar and nicotine content (Table 4-8), although these decreased risks are still substantially higher than the risk to nonsmokers. Similarly, it has been established that smokers of filtered cigarettes have relatively lower lung cancer risks than smokers of nonfiltered cigarettes (Table 4-9). Filters reduce the amount of tars, and hence a portion of the carcinogenic agents, in the MS inhaled by the smoker. Passive smokers, however, do not share in any benefit derived from cigarette filters (see Chapter 3) and may, in fact, be exposed to greater amounts of ETS if smokers of filtered cigarettes smoke a greater number of cigarettes to compensate for any reduction in nicotine uptake resulting from the filters (U.S. DHHS, 1986).

4.2.3. Histological Types of Lung Cancer and Associations With Smoking

A number of epidemiologic studies have also examined the association between various histological types of lung cancer and smoking. The results of some of these investigations are summarized in Table 4-10. Problems in interpreting the results of such studies include differences in the nomenclature, criteria, and verification of tumor classification; inadequacy of some specimens; and the small size of many of the patient groups, resulting in unstable risk

Table 4-4. Relationship between risk of lung cancer and duration of smoking in men, based on available information from cohort studies

Reference	Duration of smoking (years)	Standardized mortality ratio (no. of observed deaths)	Approximate annual excess death rate (%)[1]
Weir and Dunn (1970)	1-9	1.13	0.002 (0.001)
	10-19	6.45	0.09 (0.05)
	20+	8.66	0.12 (0.08)
	Nonsmokers	1.0	0
Cederlöf et al. (1975)	1-29	1.8 (5)	0.01 (0.008)
	>30	7.4 (23)	0.1 (0.06)
	Nonsmokers	1.0 (7)	0

[1]The mortality ratio among nonsmokers was assumed to be 15.6 per 100,000 per year, as in the American Cancer Society 25-state study. Figures in parentheses were computed by the IARC working group, applying the British doctors' mortality rate among nonsmokers (10.0/100,000 per year).

Source: IARC, 1986.

Table 4-5. Lung cancer mortality ratios for males, by age of smoking initiation--prospective studies

Study	Age of smoking initiation in years	Mortality ratio
ACS 25-state study	Nonsmoker	1.00
	25+	4.08
	20-24	10.08
	15-19	19.69
	Under 15	16.77
Japanese study	Nonsmoker	1.00
	25+	2.87
	20-24	3.85
	Under 20	4.44
U.S. veterans study	Nonsmoker	1.00
	25+	5.20
	20-24	9.50
	15-19	14.40
	Under 15	18.70
Swedish study	Nonsmoker	1.00
	19+	6.50
	17-18	9.80
	Under 16	6.40

Source: U.S. DHHS, 1982.

Table 4-6. Relationship between risk of lung cancer and number of years since stopping smoking, in men, based on available information from cohort studies

Reference	No. of years since stopping smoking	Mortality ratio (no. of observed deaths)
ACS 25-state study (Hammond, 1966)	1-19 cig./day	
	Current smokers	6.5 (80)
	<1	7.2 (3)
	1-4	4.6 (5)
	5-9	1.0 (1)
	10+	0.4 (1)
	Nonsmokers	1.0 (32)
	20+ cig./day	
	Current smokers	13.7 (351)
	<1	19.1 (33)
	1-4	12.0 (33)
	5-9	7.2 (32)
	10+	1.1 (5)
	Nonsmokers	1.0 (32)
Swedish study (Cederlöf et al., 1975)	<10	6.1 (12)
	>10	1.1 (3)
	Nonsmokers	1.0 (7)
British doctors study (Doll and Peto, 1976)	Current smokers	15.8 (123)
	1-4	16.0 (15)
	5-9	5.9 (12)
	10-14	5.3 (9)
	15+	2.0 (7)
	Nonsmokers	1.0 (7)
Rogot and Murray (1980)	Current smokers	11.3 (2,609)
	<5	18.8 (47)
	5-9	~7.5 (86)
	10-14	~5.0 (100)
	15-19	~5.0 (115)
	20+	2.1 (123)
	Nonsmokers	1.0 NA

NA = not available.

Source: IARC, 1986.

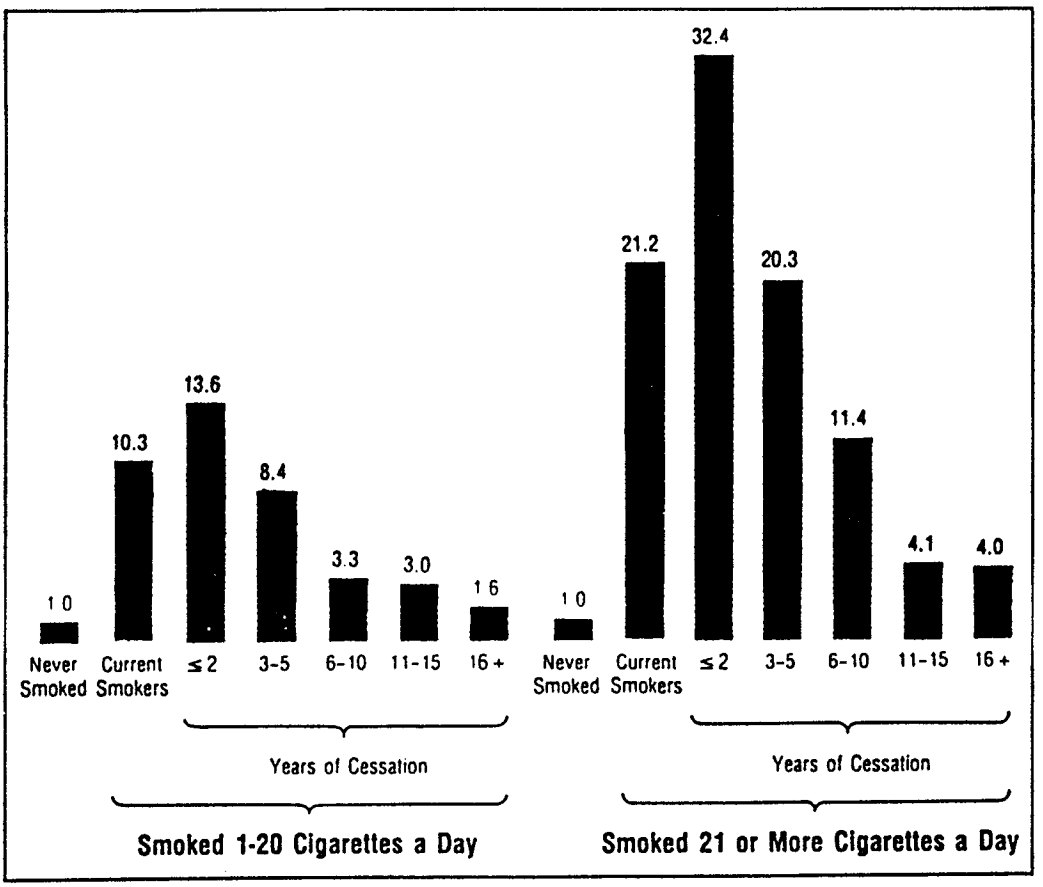


Figure 4-3. Relative risk of lung cancer in ex-smokers, by number of years quit, women, Cancer Prevention Study II.

Source: Garfinkel and Silverberg, 1991.

Table 4-7. Relative risks of lung cancer in some large cohort studies among men smoking cigarettes and other types of tobacco

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
ACS 9-state study[1]	Never smoked	1.0	12.8	15
	Occasionally only	1.5	19.2	8
	Cigarettes only	9.9	27.2	249
	Cigars only	1.0	13.1	7
	Pipes only	3.0	38.5	18
	Cigarettes + other	7.6	97.7	148
	Cigars + pipes	0.6	7.3	3
Canadian veterans study	Nonsmokers	1.0		7
	Cigarettes only	14.9		325
	Cigars only	2.9		2
	Pipe only	4.4		18
	Ex-smokers	6.1		18
ACS 25-state study[1]	Never smoked	1.0	12	49
	Cigarettes only	9.2	111	719
	Cigars only	1.9	22	23
	Pipes only	2.2	27	21
	Cigarettes + other	7.4	89	336
	Cigars + pipes	0.9	11	11
Swedish study[1]	Nonsmokers	1.0		7
	Cigarettes only	7.0		28
	Cigarettes + pipe	10.9		27
	Pipe only	7.1		31
	Cigars only	9.2		6
	Ex-smokers	6.1		12

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Table 4-7. (continued)

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
British doctors study	Nonsmokers	1.0	10	
	Current smokers	10.4	104	
	Cigarettes only	14.0	140	
	Pipes and/or cigars only	5.8	58	
	Cigarettes + other	8.2	82	
	Ex-smokers	4.3	43	
U.S. veterans study[1]	Nonsmokers	1.0		2,609
	Cigarettes	11.3		1,095
	Cigarettes only	12.1		41
	Cigars only	1.7		32
	Pipes only	2.1		517
	Ex-cigarette smokers	4.0		
Norwegian study[1]	Nonsmokers	1.0		7
	Cigarettes	9.7		88
	Cigarettes only	9.5		70
	Pipes or cigars only	2.6		12
	Ex-smokers	2.8		11

[1]Figures given in original report.

Source: IARC, 1986.

Table 4-8. Age-adjusted lung cancer mortality ratios for males and females, by tar and nicotine (T/N) in cigarettes smoked

	Males	Females
High T/N[1]	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

[1]The mortality rate for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.

Source: U.S. DHHS, 1982.

Table 4-9. Relative risk for lung cancer by type of cigarette smoked (filter vs. nonfilter), in men, based on cohort and case-control studies

Reference	Type of study	Relative risk
Hawthorne and Fry (1978)	Cohort	0.8
Rimington (1981)	Cohort	0.7
Bross and Gibson (1968)	Case-control	0.6
Wynder et al. (1970)	Case-control	0.6
Dean et al. (1977)	Case-control	0.5

Source: IARC, 1986.

Table 4-10. Main results of studies dealing with the relationship between smoking and different histological types of lung cancer

Reference	Histological type	Results						Comments
Doll et al. (1957)		Sex	No. of cases	Relative risk				Nonsmokers, 1.0 (RR) No. observed
				Amount of tobacco smoked (g)				
				<5	5-14	15-24	25+	
	Kreyberg I	M	829	4.7	10.6	14.3	25.4	3
		F	32	1.0	1.7	8.3		16
	Kreyberg II	M	38	0.5	0.8	1.2	1.1	2
		F	8	1.1	2.3	4.1		5
Hammond and Horn (1958b)		Relative risk no. of packs/day						Nonsmokers, 1.0. Only regular smokers considered
		<½		½-1		1+		
	Adenocarcinoma	2.0		2.5		7.0		
	Other types	16.3		25.5		88.0		
Doll and Hill (1964a)		Death rate per 1,000 Amount of tobacco smoked (g)						Men only
		Ex-smokers		1-14	15-24	25+		
	Squamous-cell carcinoma	0.09		0.22	0.33	0.45		
	Small-cell and anaplastic carcinoma	0.05		0.10	0.20	0.38		
	Adenocarcinoma	0.03		0.03	0.12	0.07		

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Table 4-10. (continued)

Reference	Histological type	Results					Comments
Haenszel and Taeuber (1964)		Standardized mortality ratio					Women only; standardized mortality ratio; total group, 1.00
		Never-smokers	Ex-Smokers	Occasional cigarette smokers	Regular cigarette smokers		
					<1 pack/day	>1 pack/day	
	Adenocarcinoma	0.78	0.35	2.46	1.17	7.50	
	Squamous-cell and undifferentiated carcinoma	0.59	0.52	1.15	2.19	8.58	
Hanbury (1964)		No. of cases (%)					Women only
		"Heavy" and "medium" smokers		Nonsmokers and "remainder"			
	Small-cell carcinoma	18 (47)		21 (34)			
	Undifferentiated carcinoma	9 (24)		14 (23)			
	Squamous-cell carcinoma	9 (24)		12 (19)			
	Adenocarcinoma	2 (5)		15 (24)			

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Table 4-10. (continued)

Reference	Histological type	Total no. of cases	Results										Comments
Vincent et al. (1965)			Number of cigarettes smoked/day										Women only
			None		1-20		21-40		41+		Unknown		
			No.	%	No.	%	No.	%	No.	%	No.	%	
	Squamous-cell carcinoma	19	10	53	3	16	2	10	2	10	2	10	
	Small-cell carcinoma	17	2	12	7	41	6	35	2	12	0	0	
	Adenocarcinoma	64	51	80	6	9	4	6	0	0	3	5	
	Undifferentiated	22	12	54	4	18	6	27	0	0	0	0	
	Others	41	32	78	8	20	1	2	0	0	0	0	
		163	107	66	28	17	19	12	4	2	5	3	

Wynder et al. (1970)	Sex	No. (%)		Heavy = 41+ cigarettes/day
		Cigarette smokers	Heavy smokers	
Kreyberg I	M	191 (91.0)	59 (29.9)	
	F	24 (80.0)	3 (12.0)	
Kreyberg II	M	61 (82.4)	9 (14.1)	
	F	21 (58.3)	1 (4.8)	
Controls	M	199 (47.4)	26 (9.8)	
	F	53 (40.2)	3 (5.4)	

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Table 4-10. (continued)

Reference	Histological type	Results			Comments
Deaner and Trummer (1970)		Pack-years	Number of tumors	Smokers	
	Undifferentiated carcinoma	40	40	40 (100%)	
	Adenocarcinoma	12	19	13 (68%)	
	Squamous-cell carcinoma	52	9	9 (100%)	
Weiss et al. (1972)		Death rate per 1,000 man-years of observation (adjusted for age and race)			
		No. of cigarettes/day			
		1-10	10-19	20+	
	Squamous-cell carcinoma				
	Well differentiated	-	0.8	2.1	
	Poorly differentiated	0.7	0.4	1.0	
	Small-cell carcinoma	-	0.3	0.7	
	Adenocarcinoma	-	0.6	1.0	
Vincent et al. (1977)		No. of cigarettes smoked/day			
		0	1-20	21-40	41+	Other
	Squamous-cell carcinoma	14	219	110	120	16
	Adenocarcinoma	28	101	66	53	7
	Small-cell carcinoma	4	103	62	56	6
	Large-cell carcinoma	2	40	32	33	0
	Bronchiolo-alveolar carcinoma	6	20	9	6	0
	Mixed	0	9	5	5	0
	Other	6	30	19	17	4

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Table 4-10. (continued)

Reference	Histological type	Results							Comments
Chan et al. (1979)		Smoking category (kg tobacco smoked during lifetime)							Women only
			<100		100-199		>200		
		Non-smokers	Manufactured	All	Manufactured	All	Manufactured	All	
	Squamous-cell and small-cell carcinomas	1.0	3.6	3.4	3.7	4.2	2.6	4.1	
	Adenocarcinoma	1.0	1.9	1.4	1.4	1.8	1.6	1.7	
Joly et al. (1983)		Relative risk by duration of smoking (years)							Nonsmokers, 1.0
		Men				Women			
		1-29	30-39	40-49	50+	1-29	30-39	40-49	50+
	Squamous-cell carcinoma	15.0	15.9	39.5	42.2	4.4	9.4	31.4	51.9
	Adenocarcinoma	2.0	3.2	5.3	5.7	2.1	2.7	4.7	4.0
	Undifferentiated carcinoma	26.0	26.4	40.7	50.0	3.9	15.6	20.6	28.3
	Poorly differentiated carcinoma	6.4	7.7	10.8	10.2	3.2	7.8	5.6	13.1

Source: IARC, 1986.

estimates, particularly in women. There are four major histological types of lung cancer: squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma, and large-cell undifferentiated carcinoma. Sometimes two broad categories--Kreyberg Group I, containing squamous-cell and small-cell carcinomas, and Kreyberg Group II, containing all other epithelial lung cancers, including adenocarcinomas and large-cell undifferentiated carcinomas--are used for classification. The majority of the studies demonstrate an increase in the risk for lung cancer with increasing amount smoked for all four major histological groups in both males and females. The slope of the gradient for adenocarcinomas, however, is shallower than the slopes for the other types.

4.2.4. Proportion of Risk Attributable to Active Smoking

Table 4-11 presents data on the proportion of lung cancer deaths attributable to smoking in various countries. Differences by sex and between countries largely correlate with differences in the proportion of smokers within these populations and the duration and intensity of cigarette usage. In the early 1960s, 50% of U.S. men and 30% of U.S. women smoked, although these proportions have been declining in recent years (Garfinkel and Silverberg, 1991).

In the United States, deaths from lung cancer currently represent one-quarter of all cancer deaths. The American Cancer Society predicted there would be 143,000 lung cancer deaths in 1991 (Garfinkel and Silverberg, 1991). Over 85% of this lung cancer mortality is estimated to be attributable to tobacco smoking. In other words, the overwhelming majority of lung cancer deaths, which are a significant portion of all cancer deaths, result from smoking. The strong association between smoking and lung cancer and the dose-response relationships, with effects observable at low doses and no evidence of a threshold, make it highly plausible that passive smoking also causes lung cancer in humans.

4.3. LIFETIME ANIMAL STUDIES

The human evidence for the carcinogenicity of tobacco smoke is corroborated in experimental animal bioassays. The main animal evidence is obtained from inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of SS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments.

Negative responses in short-term animal studies (e.g., 60 to 90 days) are not reliable indicators of the carcinogenic potential of a compound because of the long latency period for cancer development. Long-term animal studies at or near the maximum tolerated dose level are used to ensure an adequate power for the detection of carcinogenic activity (U.S. EPA, 1986a).

Table 4-11. Lung cancer deaths attributable to tobacco smoking in certain countries

Country	Year	No. of deaths[1]	Expected deaths in nonsmokers[2]	Crude rate in persons aged 35+		AC[3]	AP[4]
				Observed	In non-smokers		
Canada							
Men	1978	6,435	556	142.8	11.8	5,762	0.9
Women	1978	1,681	487	34.0	9.9	1,194	0.71
England and Wales							
Men	1981	26,297	1,576	228.5	13.3	24,720	0.94
Women	1981	8,430	1,663	63.3	12.4	6,767	0.80
Japan							
Men	1981	16,638	2,868	64.8	10.7	13,184	0.83
Women	1981	6,161	2,593	21.0	8.9	3,568	0.58
Sweden							
Men	1981	1,777	301	85.0	14.0	1,476	0.83
Women	1981	654	281	28.0	12.3	373	0.57
USA							
Men	1979	72,803	5,778	166.7	12.7	67,024	0.92
Women	1979	25,648	5,736	50.0	11.1	19,912	0.78

[1]From the Global Epidemiological Surveillance and Health Situation Assessment data bank of WHO.
[2]Calculated by IARC, 1986. Slightly overestimates number of expected deaths.
[3]AC, number of cases attributable to smoking.
[4]AP, proportion of cases attributable to smoking.

Source: IARC, 1986.

4.3.1. Inhalation Studies

Although evidence of the carcinogenicity of cigarette smoke originated in humans, attempts were made to develop an inhalation model for smoking in experimental animals in order to study the carcinogenicity of various tobacco products. Such inhalation studies are difficult to conduct, however, because laboratory animals are reluctant to inhale cigarette smoke and will adopt shallow breathing patterns in response to aerosols and irritants. Furthermore, rodents are obligatory nose-breathers, and the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ between rodents and humans. Because of these distinctions, laboratory animals and humans are likely to have different deposition and exposure patterns for the various cigarette smoke components in the respiratory system. For example, rodents have extensive and complex nasal turbinates where significant particle deposition could occur, decreasing exposure to the lung.

The Syrian golden hamster has been the most useful animal inhalation model found so far for studying smoking-induced carcinogenesis. It is more tolerant of tobacco smoke than mice and rats and is relatively resistant to respiratory infections. The hamster also has a low background incidence of spontaneous pulmonary tumors and is, in fact, refractory to the induction of lung cancers by known carcinogenic agents. The inhalation of tobacco smoke by the hamster does, however, induce carcinomas of the larynx. In one study (Dontenwill et al., 1973), three groups of 80 male and 80 female Syrian golden hamsters were exposed for 10 minutes to air-diluted cigarette smoke (1:15) once, twice, or three times daily, 5 days per week, for their lifetimes. Preinvasive carcinomas of the upper larynx were detected in 11.3%, 30%, and 30.6% of the animals, respectively, and invasive carcinomas were found in 0.6%, 10.6%, and 6.9%, respectively. No laryngeal tumors were observed in control animals. In another experiment, exposure for 59 to 80 weeks to an 11% or 22% cigarette smoke aerosol twice daily for 12 minutes resulted in laryngeal carcinomas in 3 of 44 and 27 of 57 animals, respectively, providing some evidence of a dose-response relationship for the induction of carcinoma of the larynx by cigarette smoke (Bernfeld et al., 1979). Bernfeld et al. suggest that the greater deposition of tar per unit of surface area in the larynx compared to the lung may explain the high yield of laryngeal cancers and lack of lung tumors in this animal model.

4.3.2. Intrapulmonary Implantations of Cigarette Smoke Condensates

Because of the difficulties with inhalation studies of cigarette smoke, some in vivo studies examine the carcinogenicity of cigarette smoke condensate (CSC) collected from smoking machines. CSC assays may not, however, reveal all of the carcinogenic activity of actual cigarette smoke, because these condensates lack most of the volatile and semivolatile components of whole

smoke. In lifetime rat studies, intrapulmonary implants of MS condensate in a lipid vehicle cause a dose-dependent increase in the incidence of lung carcinomas (Stanton et al., 1972; Dagle et al., 1978).

SS condensates have also demonstrated carcinogenicity when implanted into rat lungs (Grimmer et al., 1988). SS emitted by a smoking machine was separated into condensate fractions containing the semivolatiles, the polycyclic aromatic hydrocarbon (PAH)-free particulates and the PAHs with two or three rings, or the PAHs with four or more rings. These fractions were implanted into female Osborne-Mendel rats, following the procedure of Stanton et al. (1972), at a dose level of one cigarette per animal. At the end of the lifetime study, none of the 35 rats in each of the untreated control, vehicle control, or semivolatile-exposed groups had lung carcinomas. In the group exposed to the fraction containing PAH-free particulates and PAHs with 2 or 3 rings, there was 1 lung carcinoma in 35 animals. In the group exposed to the fraction comprising PAHs with 4 or more rings, there were 5 lung carcinomas in 35 rats. An additional group that was exposed to a dose of 0.03 mg benzo[a]pyrene (BaP) per rat exhibited 3 lung carcinomas in 35 animals. The condensate fraction containing BaP and the other PAHs with four or more rings from the SS generated by a single cigarette contains about 100 ng of BaP. Assuming a linear, nonsynergistic dose-response relationship, this would suggest that less than 1% of the total carcinogenicity of that condensate fraction can be attributed to the BaP present in the smoke.

4.3.3. Mouse Skin Painting of Cigarette Smoke Condensates

In addition, numerous studies have shown that when MS condensate suspended in acetone is chronically applied to mouse skin, significant numbers of the mice develop papillomas or carcinomas at the site of application (e.g., Wynder et al., 1957; Davies and Day, 1969). Mouse skin studies have also demonstrated that MS condensate has both tumor-initiating and tumor-promoting capabilities (Hoffman and Wynder, 1971).

One mouse skin painting study examined the carcinogenicity of SS condensate (Wynder and Hoffman, 1967). Cigarette tar from SS deposited on the funnel of a smoking machine was suspended in acetone and administered to mouse skin. Fourteen of thirty mice developed skin papillomas, and 3 of 30 developed carcinomas. In a parallel assay in the same study, a suspension of MS condensate applied to deliver a comparable amount of condensate to the skin of 100 mice yielded benign skin tumors in 24 and malignant tumors in 6 of the mice. This suggests that the condensate of SS has greater mouse skin tumorigenicity per unit weight than that of MS.

4.4. GENOTOXICITY

Supportive evidence for the carcinogenicity of tobacco smoke is provided by the demonstration of genotoxicity in numerous short-term assays. Extensive reviews of these studies can be found in IARC (1986) and DeMarini (1983); only the highlights are presented here. A few studies deal with whole smoke, but most examine CSC. Tobacco smoke is genotoxic in virtually every in vitro system tested, providing overwhelming supportive evidence for its carcinogenic potential.

In *Salmonella typhimurium*, for example, Basrur et al. (1978) found that both whole MS and MS condensates from various types of tobacco were mutagenic in the presence of a metabolic activating system. SS (Ong et al., 1984) and extracts of ETS collected from indoor air (Löfroth et al., 1983; Alfheim and Ramdahl, 1984; Lewtas et al., 1987; Ling et al., 1987; Löfroth et al., 1988) also exhibit mutagenic activity in this bacterium. Claxton et al. (1989) found that SS accounted for approximately 60% of the total *S. typhimurium* mutagenicity per cigarette--40% from the SS particulates and 20% from the semivolatiles. The highly volatile fraction, from either MS or SS, was not mutagenic.

Similarly, cigarette smoke produced mitotic gene conversion, reverse mutation, and reciprocal mitotic recombination in fungi (Gairola, 1982). In addition, CSC's induce mutations, sister chromatid exchanges, and cell transformation in various mammalian cells in culture. Putnam et al. (1985) demonstrated dose-dependent increases in sister chromatid exchange frequencies in bone-marrow cells of mice exposed to cigarette smoke for 2 weeks.

4.5. SUMMARY AND CONCLUSIONS

Lung cancer mortality rates have increased dramatically over the past 60 years in males, and, more recently, in females, with increasing cigarette consumption. High relative risks for lung cancer, associated with the number of cigarettes smoked per day, have been demonstrated in countless studies, with no evidence of a threshold level of exposure. Active smoking induces all four major histological types of human lung cancer--squamous-cell carcinomas, small-cell carcinomas, large-cell carcinomas, and adenocarcinomas--all in a dose-related manner. Dose-response relationships have also been established with respect to duration of smoking. Furthermore, lung cancer risk increases with the younger the age at initiation of smoking and decreases with the longer the time since cessation of smoking. These latter trends, coupled with evidence from mouse skin painting studies, suggest that tobacco smoke has both tumor-initiating and tumor-promoting capabilities.

Inhalation studies in hamsters confirm that MS is carcinogenic to the respiratory tract. In addition, mouse skin painting experiments and intrapulmonary implantations in rats have demonstrated the carcinogenicity of condensates from both MS and SS (the primary component of ETS), with SS condensate having a greater potency than MS condensate in mouse skin painting studies. Numerous genotoxicity tests contribute supporting evidence for the carcinogenic potential of MS and SS smoke and smoke condensates. The mutagenicity of ETS and its extracts has also been established. One study found that SS accounted for 60% of the total mutagenicity per cigarette.

As discussed in Chapter 3, MS and ETS are qualitatively similar in composition, and both contain numerous known or suspected human carcinogens. ETS constituents include essentially all of the same carcinogens found in MS, and many of these appear in greater amounts in SS, and hence, in ETS, than in MS, per unit of tobacco burned. This quantitative comparison is consistent with the observation noted above that SS condensates apparently have even greater carcinogenic potential than MS condensates.

The unequivocal causal association between tobacco smoking and lung cancer in humans with dose-response relationships extending down to the lowest exposure categories, as well as the corroborative evidence of the carcinogenicity of both MS and ETS provided by animal bioassays and in vitro studies and the chemical similarity between MS and ETS (Chapter 3), clearly establish the plausibility that ETS is also a human lung carcinogen. In addition, biomarker studies verify that passive smoking results in detectable uptake of tobacco smoke constituents by nonsmokers, affirming that ETS exposure is a public health concern (Chapter 3).

In fact, these observations are sufficient in their own right to establish the carcinogenicity of ETS to humans. According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria (that) must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

Given the strong dose-related associations, with high relative risks consistently observed across numerous independent studies from several countries, and the biological plausibility provided by ancillary evidence of the genotoxicity and animal carcinogenicity of MS and by

knowledge of the existence of many specific carcinogenic components within MS, confounding, bias, and chance can all be ruled out as possible explanations for the observed association between active smoking and lung cancer. Therefore, under the EPA carcinogen classification system, MS would be categorized as a Group A (known human) carcinogen. Furthermore, the extensive chemical and toxicological similarities between SS and MS, detailed in Sections 3.2, 4.3, and 4.4, strongly infer that SS is also capable of causing lung cancer in humans, as was documented for MS in Section 4.2. Thus, under EPA's carcinogen classification system, SS also belongs in Group A. Finally, because ETS is composed of SS and exhaled MS, and because ETS is known to be inhaled and absorbed into the body (Section 3.3.2), ETS would similarly be categorized as a Group A carcinogen.

In addition, there exists a vast body of epidemiologic data dealing specifically with lung cancer and exposure to ETS. These data should also be examined in the interest of weighing all the available evidence, as recommended by EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a), both for hazard identification and exposure-response assessment. The rapid dilution of both SS and exhaled MS into the environment and changing phase distributions of ETS components over time raise some questions about the carcinogenic potential of ETS under actual environmental exposure conditions. Furthermore, while MS and ETS may be qualitatively comparable, active smoking data do not constitute a good basis for quantitative estimation of the health effects of passive smoking because the relative uptake and deposition between active and passive smokers of the agent(s) responsible for these effects are not known (see Chapters 2 and 6). Provided the epidemiologic studies are of sufficient power and adequate study design, this database can offer unique information on the actual lung cancer risk to nonsmokers from exposure to true ambient levels of ETS. The epidemiologic evidence for the human lung carcinogenicity associated specifically with ETS is the subject of Chapter 5. These epidemiologic data are then used as the basis for the calculation of population risk estimates for lung cancer from passive smoking in Chapter 6.

5. HAZARD IDENTIFICATION II: INTERPRETATION OF EPIDEMIOLOGIC STUDIES ON ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER

5.1. INTRODUCTION

The Centers for Disease Control attributed 434,000 U.S. deaths in 1988 to smoking (CDC, 1991a). Major disease groups related to smoking mortality include lung cancer, chronic obstructive pulmonary disease, coronary heart disease, and stroke, with smoking accountable for an estimated 87%, 82%, 21%, and 18% of total deaths, respectively. Lung cancer alone accounted for about 25% to 30% of the total smoking mortality, with some 100,000 deaths. The age-standardized annual lung cancer mortality rates for 1985 are estimated at 12 per 100,000 for females and 15 per 100,000 for males who never smoked but 130 per 100,000 for female cigarette smokers and 268 per 100,000 for male cigarette smokers, a relative risk of 10.8 and 17.4, respectively (Garfinkel and Silverberg, 1991).

Chapter 4 discusses the biological plausibility that passive smoking also may be a risk factor for lung cancer because of the qualitative similarity of the chemical constituency of sidestream smoke, the principal source of environmental tobacco smoke (ETS), and mainstream smoke taken in during the act of "puffing" on a cigarette, and because of the apparent nonthreshold nature of the dose-response relationship observed between active smoking and lung cancer. Although the relative risk of lung cancer from passive smoking would undoubtedly be much smaller than that for active smoking, the ubiquity of ETS exposure (Chapter 3) makes potential health risks worth investigating.

This chapter analyzes the data from the large number of epidemiologic studies on ETS and lung cancer that contain data on the effects of ETS on never-smoking women. Although some of the studies involve male nonsmokers and former smokers of both sexes, the female never-smokers comprise the large majority of the database--more than 3,000 cases and 6,000 controls in the 27 case-control studies and almost 300,000 female never-smokers followed in the 4 cohort studies. Whenever study data are separated by sex and smoking status, women never-smoker results are used. The use of a more homogeneous group allows more confidence in the results of combined study analyses. All of the studies used provide data on adult home exposure to ETS. Some also provide information on childhood and/or workplace exposure, but there is far less information on these exposures; therefore, in order to develop one large database for analysis, only the female exposures from spousal smoking are considered. The exposure surrogate used is a report of the husband's smoking status. Wherever a measure of the amount of exposure to husband's smoking is available, additional analyses are performed to examine effects in the highest exposure groups (Section 5.3.3.2) and dose-response relationships (Section 5.3.3.3). Virtually all of the 31 studies

available classify never-smoking women as "exposed" or "unexposed" to ETS based on self- or proxy-reported smoking in the subject's environment, usually according to whether or not a woman is married to a smoker. In addition, 17 studies provide sufficient information for highest exposure group and exposure-response analyses. Other analyses of the data include adjusting for the potential upward bias of smoker misclassification (Section 5.2.2); examining confounders, effect modifiers, and sources of potential bias (Section 5.4); and pooling qualitatively higher ranked studies (Section 5.5). It is hoped that by analyzing the data in several different ways, a clear picture will emerge (Section 5.6).

Throughout this chapter, one-tailed tests of significance ($p = 0.05$) are used, which increases the statistical ability (power) to detect an effect. The 90% confidence intervals used for the analyses performed are consistent with the use of the one-tailed test. The justification for this usage is based on the *a priori* hypothesis (from the plausibility of a lung cancer effect documented in Chapters 3 and 4) that a positive association exists between exposure to ETS and lung cancer.

Epidemiologic evidence of an association between passive smoking and lung cancer first appeared 10 years ago in a prospective cohort study in Japan (Hirayama, 1981a) and a case-control study in Greece (Trichopoulos et al., 1983). Both studies concluded that the lung cancer incidence and mortality in nonsmoking women was higher for women married to smokers than for those married to nonsmokers. Although there are other sources of exposure to ETS, particularly outside the home, the assumption is that women married to smokers are exposed to more tobacco smoke, on average, than women married to nonsmokers. These two studies, particularly the cohort study from Japan, evoked considerable critical response. They also aroused the interest of public health epidemiologists, who initiated additional studies.

At the request of two Federal agencies--the U.S. Environmental Protection Agency (Office of Air and Radiation) and the U.S. Department of Health and Human Services (Office of Smoking and Health)--the National Research Council (NRC) formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on the health consequences. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail and includes summary analyses of the evidence from 10 case-control and 3 cohort (prospective) studies. It concludes, "Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers."

The NRC committee was particularly concerned about the potential bias in the study results caused by the fact that current and former smokers may have incorrectly reported themselves as lifelong nonsmokers (never-smokers). Using reasonable assumptions for misreported smoking habits, the committee determined that a plausible range for the true relative

risk is 1.15 to 1.35, with 1.25 the most likely value. When these relative risks also are corrected for background exposure to ETS to make the risk relative to a baseline of zero ETS exposure, the resultant estimate is 1.42, with a plausible range of 1.24 to 1.61.

Two other major reports on passive smoking have appeared: the Surgeon General's report on the health consequences of passive smoking (U.S. DHHS, 1986) and the report on methods of analysis and exposure measurement related to passive smoking by the International Agency for Research on Cancer (IARC, 1987a). The Surgeon General's report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS lead to the conclusion that involuntary smoking is a cause of lung cancer.

The IARC committee emphasized issues related to the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. Included in the 1987 IARC report is a citation from the summary statement on passive smoking of a previous IARC report that the epidemiologic evidence available at that time (1985) was compatible with either the presence or absence of lung cancer risk. Based on other considerations related to biological plausibility, however, it concludes that passive smoking gives rise to some risk of cancer. Specifically, the report (IARC, 1986) states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive smoking," and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens . . . leads to the conclusion that passive smoking gives rise to some risk of cancer.

In the years since those reports, the number of studies available for analysis has more than doubled. There are now 31 epidemiologic studies available from eight different countries, listed in Table 5-1. Twenty-seven studies employ case-control designs, denoted by the first four letters of the first author's name for convenient reference, and four are prospective cohort studies, distinguished by the designation "(Coh)." Six case-control studies, FONT (USA), JANE (USA), KALA (Greece), LIU (China), SOBU (Japan), and WUWI (China), have been published as recently as 1990. The small cohort study from Scotland (Gillis et al., 1984) has been updated and is now included under the name HOLE(Coh); another small cohort study on Seventh-Day Adventists in the United States, an unpublished dissertation, is included as BUTL(Coh). The abstracts for a second case-control study by Kabat and Wynder and a new one by Stockwell and colleagues are included in Section A.4, but insufficient information is available to include their results.

Table 5-1. Epidemiologic studies on ETS and lung cancer in this report and tier ranking

Study	Tier[1]	Country	Within country	References
AKIB	2	Japan	Hiroshima	Akiba et al. (1986)
BROW	3	United States	Colorado	Brownson et al. (1987)
BUFF	3	United States	Texas	Buffler et al. (1984)
CHAN	4	Hong Kong		Chan and Fung (1982)
CORR	2	United States	Louisiana	Correa et al. (1983)
FONT	1	United States	Five metro areas	Fontham et al. (1991)
GAO	3	China	Shanghai	Gao et al. (1987)
GARF	2	United States	New Jersey, Ohio	Garfinkel et al. (1985)
GENG	4	China	Tianjin	Geng et al. (1988)
HUMB	2	United States	New Mexico	Humble et al. (1987)
INOU	4	Japan	Kanajawa	Inoue and Hirayama (1988)
JANE	2	United States	New York	Janerich et al. (1990)
KABA	2	United States	New York	Kabat and Wynder (1984)
KALA	1	Greece	Athens	Kalandidi et al. (1990)
KATA[2]		Japan		Katada et al. (1988)
KOO	1	Hong Kong		Koo et al. (1987)
LAMT	2	Hong Kong		Lam et al. (1987)
LAMW	3	Hong Kong		Lam (1985)
LEE	2	England		Lee et al. (1986)
LIU	4	China	Xuanwei	Liu et al. (1991)
PERS	1	Sweden		Pershagen et al. (1987)
SHIM	2	Japan	Nagoya	Shimizu et al. (1988)
SOBU	2	Japan	Osaka	Sobue (1990)
SVEN	2	Sweden	Stockholm	Svenson et al. (1989)

(continued on the following page)

Table 5-1. (continued)

Study	Tier	Country	Within country	References
TRIC	3	Greece	Athens	Trichopoulos et al. (1981, 1983)
WU	2	United States	California	Wu et al. (1985)
WUWI	4	China		Wu-Williams and Samet (1990)
BUTL(Coh)	2	United States	California	Butler (1988)
GARF(Coh)	3	United States		Garfinkel (1981)
HIRA(Coh)	2	Japan		Hirayama (1984)
HOLE(Coh)	1	Scotland	Paisley Renfrew	Hole et al. (1989)

[1]Tier rankings refer to this report's ratings of studies for utility of studying the association of ETS and lung cancer, where "1" is highest (see Section 5.5 and Section A.3).
[2]KATA has no tier number because the odds ratio cannot be calculated.

Because of coincidental timing, the 1986 reports of the Surgeon General and the NRC review approximately the same epidemiologic studies. More specifically, the NRC report includes nine of the studies shown in Table 5-1: AKIB, CHAN, CORR, GARF, KABA, KOO, LEE, PERS, and TRIC; WU was available but not included because the crude data were not reported. (Crude data consist of the number of exposed and unexposed subjects among lung cancer cases and controls, where a subject is typically classified as exposed to ETS if married to a smoker.) The NRC also excluded an earlier version of the KOO study and the studies by Knoth et al. (1983) (no reference population was given), Miller (1984) (did not report on lung cancers separately), and Sandler et al. (1985) (included very few lung cancers). Aside from WU, these studies also are omitted from this report for the same reasons.

Tables 5-2 and 5-3 provide an overview of some descriptive features of the individual ETS studies included in this report. The studies are grouped by country in Table 5-2, which indicates the time period of data collection in each study, sample size, and prevalence of ETS exposure for each study. The geographical distribution of the current epidemiologic evidence is diverse. By country, the number of studies and its percentage of the total number of studies over all countries is as follows: China (4, 13%), England (1, 3%), Greece (2, 6%), Hong Kong (4, 13%), Japan (6, 19%), Scotland (1, 3%), Sweden (2, 6%), and United States (11, 35%). (One of the

Table 5-2. Studies by location, time, size, and ETS exposure

Country	Study	Accrual[1] period	Size[2] Cases	Size[2] Controls	ETS exposure (%)[3] Cases	ETS exposure (%)[3] Controls
Greece	KALA	1987-89	90	116	71	60
Greece	TRIC	1978-80	40	149	73	52
Hong Kong	CHAN	1976-77	84	139	60	53
Hong Kong	KOO	1981-83	86	136	59	49
Hong Kong	LAMT	1983-86	199	335	58	45
Hong Kong	LAMW	1981-84	60[4]	144[4]	62[4]	44[4]
Japan	AKIB	1971-80	94	270	78	70
Japan	HIRA(Coh)	1965-81	— 91,540 —		—— 76 ——	
Japan	INOU	1973-83	22	47	82	64
Japan	SHIM	1982-85	90	163	58	56
Japan	SOBU	1986-88	144	731	56	54
USA	BROW	1979-82	19	47	21	15
USA	BUFF	1976-80	41	196	80	84
USA	BUTL(Coh)	1976-82	— 9,207[5] —		—— 34[5] ——	
USA	CORR	1979-82	22	133	64	46
USA	FONT	1985-88	420	780[6]	70	63[6]
USA	GARF	1971-81	134	402	67	61
USA	GARF(Coh)	1959-72	— 176,739 —		—— 72 ——	
USA	HUMB	1980-84	20	162	75	56
USA	JANE	1982-84	191	191	*[7]	60[7]
USA	KABA	1961-80	24	25	54	60
USA	WU	1981-82	29[8]	62[8]	*	*
W. Europe						
Scotland	HOLE(Coh)	1972-85	— 1,784 —		—— 73 ——	
England	LEE	1979-82	32	66	69	68

(continued on the following page)

Table 5-2. (continued)

Country	Study	Accrual[1] period	Size[2] Cases	Size[2] Controls	ETS exposure (%)[3] Cases	ETS exposure (%)[3] Controls
W. Europe (continued)						
Sweden	PERS	1961-80	67	*	49	*
Sweden	SVEN	1983-85	34	174	71	66
China	GAO	1984-86	246	375	77	74
China	GENG	1983	54	93	63	44
China	LIU	1985-86	54	202	83	87
China	WUWI	1985-87	417	602	49	55

[1]Time during which cases occurred.
[2]Number of subjects included in ETS analyses; where numbers differ for spousal smoking and other exposures, those for spousal smoking are given.
[3]Spousal smoking unless otherwise noted.
[4]Adenocarcinoma only. Data for all cell types were available only for general passive smoke exposure, which showed 77% of 75 cases and 56% of 144 controls exposed.
[5]Figure pertains to "spouse pairs" cohort, which is of principal interest regarding ETS; a subgroup of this cohort comprised the "ASHMOG" cohort.
[6]Figure is for population controls; study also included 351 colon cancer controls (66% exposed).
[7]ORs but no exposure prevalences are presented for spousal smoking in the source. The value shown for controls is taken from KABA, as closest to JANE in time and location; no exposure percentage is assumed for cases.
[8]Adenocarcinoma only. Analyses for other cell types included smokers while adjusting for smoking status.

*Data not available.

Table 5-3. Case-control studies of ETS: characteristics

Study	Percentage proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
AKIB	90	88	70.2 35-95	* *	Atomic bomb survivor population	Age, sex, residence, vital status, med. subject[3]	No
BROW	69	39	66.3	68.2	Cancer cases[4]	Age, sex	No[5]
BUFF	82	76	30-79	30-79	Cancer cases[6]	Age, sex	No[5]
CHAN	*	*	39-70	39-70	Orthopedic patients	Matched but variables unspecified	No[5]
CORR	*	*	*	*	Hospital patients[7]	Age (± 5), sex, race	No[5]
FONT	34	0-10[8]	20-79	20-79	Cancer cases; general population	Age, (for cancer controls) race	Yes
GAO	0	*	35-69	35-69	General population	Age (± 5)	No[5]
GARF	88	*	≥40	≥40	Cancer cases[9]	Age (± 5), hospital	Yes
GENG	0	0	≤65	≤65	*	Age (± 2), sex, race, marital status	No[5]
HUMB	*	*	≤85	≤85	General population	Age (± 10), sex, ethnicity	No[5]
INOU	*	*	*	*	Cerebrovas-cular disease deaths	Age, year of death (± 2.5), district	No[5]
JANE	33[10]	33[10]	67.1[10]	68.1[10]	New York State Dept. of Motor Vehicles	Age, sex, county, smoking history	Yes

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Table 5-3. (continued)

Study	Percentage proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
KABA	0	0	61.6	53.9	Patients[11]	Age (± 5), sex, race, hospital	Yes
KALA	0	0	≥35	≥35	Orthopedic patients	Sex	Yes
KATA	0	0	67.8	*	Noncancer patients	Age (± 2), sex	Yes
KOO	0	0	*	*	"Healthy"[12]	Age (± 5), residence, housing	No[5]
LAMT	0	0	*	*	"Healthy"[13]	Age (± 5), residence	No[5]
LAMW	*	*	67.5	66	Hospitalized orthopedic patients	Age, socio-economic status, residence[14]	No[5]
LEE	38[15]	38	35-74	35-74	Patients[16]	Age, sex, hospital location, time of interview	No[5,17]
LIU	0	0	52	52	General population?	Age (± 2), sex, village	Yes
PERS	*[18]	*	*[19]	*	*[20]	Age (± 1), sex	Yes
SHIM	0	0	59 35-81	58 35-81	Patients[21]	Age (± 1), hospital, admission date	Yes
SOBU	0	0	60	56	Patients	None	No
SVEN	0	0	66.3		General population	Age	No[5]

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Table 5-3. (continued)

Study	Percentage proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
TRIC	0	0	62.8	62.3	Hospitalized orthopedic patients	Age, occupation, education[14]	No[5]
WU	0	0	<76	<76	Neighbor-hood[13]	Age (± 5), sex, race	No[5]
WUWI	0	0	55.9[22]	55.4[22]	General population	Sex, age[23]	No[5]

[1]"Ca" and "Co" stand for "cases" and "controls," respectively.
[2]Single values are the average or median. Paired values are the range.
[3]Participation in RERF biennial medical examination program.
[4]Persons with cancers of bone marrow or colon in Colorado Control Cancer Registry.
[5]Not matched on personal smoking status (e.g., smoker/nonsmoker).
[6]Population-based and decedent comparison subjects selected from state and Federal records.
[7]Assorted ailments.
[8]0% for general population and 10% for colon cancer controls.
[9]Colorectal cancer.
[10]Includes males and females and long-term ex-smokers.
[11]Diseases not related to smoking.
[12]Selected from a healthy population.
[13]Living in neighborhood of matched case.
[14]"Similar" but not actually matched.
[15]Applies only to the 143 patients in the followup study.
[16]Excluding lung cancer, chronic bronchitis, ischemic heart disease, and stroke.
[17]Ongoing study modified for passive smoking.
[18]No overall percentages given.
[19]Two control groups: 15 to 65 and 35 to 85 for both cases and controls in groups 1 and 2, respectively.
[20]Two control groups were randomly chosen from the cohort under study.
[21]Patients in the same or adjacent wards with other diseases.
[22]Entire study population, including smokers.
[23]Frequency matched by 5-year age group to age distribution of cases reported in study area 2 years prior to initiation of study.

*Data not available.

studies from Japan, KATA, does not appear in most of the tables because the odds ratio cannot be calculated.) The studies differ by size, however, which has to be taken into account in analysis. There are two large cohort studies, GARF(Coh) and HIRA(Coh), conducted in the United States and Japan, respectively, and two very small ones, BUTL(Coh) and HOLE(Coh), from the United States and Scotland, respectively. There are two exceptionally large case-control studies--FONT and WUWI of the United States and China; the first was designed specifically to assess the association between ETS and lung cancer, whereas the second has broader exploratory objectives.

The accrual periods of the case-control studies are typically 2 to 4 years in length (exceptions with longer periods are AKIB [9 years], INOU [10 years], GARF [10 years], KABA [19 years], and PERS [9 years]) and occur between the early 1970s and late 1980s (exceptions are KABA [1961-1980] and PERS [1961-1980]). The two large cohort studies were conducted relatively early (GARF(Coh), 1959-72; HIRA(Coh), 1965-81). Differences in study duration or accrual period should not be consequential for hazard identification, which is the topic addressed in this chapter, but both factors affect the estimation of population risk (Chapter 6). Earlier study results are more uncertain for projection of current risk, and parameter values used for modeling are more uncertain when based on extended study periods. Table 5-2 also demonstrates variability across studies in the percentages of cases and controls classified as exposed to ETS. For example, at the extremes for U.S. studies alone, BUFF and BROW classify 84% and 15% of controls as exposed to ETS, respectively. Statistical variability and differences across subpopulations sampled are partially explanatory, but a major factor is differences between researchers' criteria for classification of subjects as exposed to ETS. This issue affects study comparability and observed values of relative risks, which affect both hazard identification and characterization of population risk.

Another example of a study feature of broad consequences in both case-control and cohort studies is the method of diagnosis or confirmation of lung cancer and exclusion of secondary lung cancers in subjects classified as having lung cancer, as shown in Table 5-4. Accurate classification of subjects vis-a-vis the presence or absence of primary lung cancer is essential to the validity of results; inaccurate classification can reduce the chance of detecting a positive association between ETS exposure and lung cancer, if it exists, by biasing the observed relative risk toward unity. (*Note*: "Relative risk" is used to mean the estimate of the true [but unknown] relative risk. For case-control studies, the estimate used is the odds ratio. For editorial convenience, "relative risk" is used for both case-control and cohort studies.)

The large majority of the studies (27 of 31 total) are of the case-control type, which are subject to more potential sources of bias than the cohort studies (see discussion in Section 5.4.1).

Table 5-4. Diagnosis, confirmation, and exclusion of lung cancer cases

Study	Diagnosis/Confirmation (%)[1] Histology		Cytology	Radio./ clinical	Other/ unspec.	Excluded secondary LC[2]
AKIB[3]	53		4	43	0	Y
BROW	———	100	———			Y
BUFF[3,4]	———	100	———			Y
CHAN[3,4]	82				18	N
CORR[3]	97				3	Y
FONT	100					Y
GAO[3,5]	43		38	19	10	Y
GARF[5]	100					Y
GENG[3]	85			4	11	N
HUMB[6,7]	———	83	———		17	Y
INOU	*		*	*	*	N
JANE[3]	99			1		Y
KABA	100					Y
KALA	48		38		14	Y
KATA	100					N
KOO	94				6	Y
LAMT	———	100	———			Y
LAMW	———	100	———			Y
LEE	*		*	*	*	N
LIU[8]	———	17	———	83	0	N
PERS	83		16		1	Y
SHIM	100					Y
SOBU	100					Y
SVEN[3]	70		29		1	Y
TRIC[3]	28		37	35		N
WU	100					Y
WUWI[3]	42		32	26		Y
BUTL(Coh)[9]		100				Y
GARF(Coh)	*		*	*		N

(continued on the following page)

Table 5-4. (continued)

Study	Diagnosis/Confirmation (%)[1] Histology	Cytology	Radio./ clinical	Other/ unspec.	Excluded secondary LC[2]
HIRA(Coh)	*	*	*		N
HOLE(Coh)[10]	*	*	*		N

[1]Figures apply to confirmation of original diagnosis when conducted.
[2]Y (for "yes") if specifically indicated; otherwise, N (for "no").
[3]Not restricted to never-smokers (contains former smokers or ever-smokers).
[4]Inconsistency in article. May be 100% histology.
[5]Diagnostic information was reviewed for study.
[6]Includes males.
[7]Available histologic specimens (17 cases) reviewed by pathologists. Poor agreement between review diagnoses and original cancer registry diagnoses (8 of 17 cases). Only reviewed cases, however, are presented in article.
[8]Includes male ever- and never-smokers and one female ever-smoker (control).
[9]Includes one former smoker.
[10]Death certificate diagnosis checked against Scottish cancer registry records.

*Data not available.

To continue the overview depicting some basic similarities and differences between studies that may affect analysis of their results, some additional characteristics of the case-control studies alone are summarized in Table 5-3. The percentage of proxy response is high for some studies, but there is little basis for assessing the direction or magnitude of potential bias from this source. The age range of subjects differs across studies, but there is insufficient information on age distributions within studies to evaluate the effect of age or to adjust for differences between studies. The source of control subjects is a potential source of bias in some studies.

The table heading "ETS sample matched" refers to whether design matching applies to the ETS subjects (the never-smokers used for ETS/lung cancer analysis). As indicated under "matched variables," controls are virtually always matched (or at least similar) to cases on age and usually on several other variables as well that the researcher suspects may affect comparability of cases and controls. The matching often refers to a larger data set than the ETS subjects only, however, because many studies included smokers and investigated a number of issues in addition to whether passive smoking is associated with lung cancer. When the data on ETS subjects are

extracted from the larger data set, matching is not retained unless smoking status was one of the matching variables.

Although matching is commonly used as a method to reduce potential confounding, effective techniques also may be implemented during analysis of the data (e.g., the use of poststratification or logistic regression adjustment for unmatched, stratified, or frequency-matched samples). Use of a method of analysis that adjusts for known or suspected confounders and factors that may interact with ETS exposure to affect risk of lung cancer is particularly important for studies that are not designated as "ETS sample matched" in Table 5-3. Even with matched data, a method of analysis that controls for confounding, such as the use of matched pairs or regression techniques, is preferable. In fact, Breslow and Day (1980, p. 32) describe the main purpose of matching in a case-control study as permitting use of efficient analytical methods to control confounding by the factors used for matching.

The analysis for hazard identification in this report follows two approaches. The first approach (Section 5.3) treats all studies equally, i.e., statistical methods are applied to all studies without regard to differences in study utility for the task of hazard identification. Differences in study size, of course, are taken into account by the statistical methods. Statistical inference includes estimation, with confidence intervals, and hypothesis testing for an effect (an increased relative risk in ETS-exposed subjects) and for an upward trend (an increase in relative risk as some measure of ETS exposure increases). The second approach (Section 5.5) is motivated by the heterogeneity of the study evidence, as described above. Study size aside, some studies have higher utility than others for assessing questions related to ETS and lung cancer and thus should be given more weight. To implement this extended data interpretation, all studies are first reviewed individually for sources of bias and confounding that might affect interpretation of results for assessing ETS and lung cancer and then assigned a tier number from 1 to 4 accordingly. Tier 1 contains those studies of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. (*Note:* Study utility does not mean study quality. Utility is evaluated with respect to the research objectives *of this report*, while the objectives of individual studies often differ.) Pooled estimates of relative risk by country are then recalculated by tiers, beginning with the studies of highest utility (Tier 1) and adding studies from Tiers 2, 3, and 4 successively to see what effect a judgment of utility has on the overall outcome in each country. The criteria used in evaluating studies and the procedure for assigning them to tiers are described in Appendix A, which also contains the individual study reviews.

The selection of the most appropriate relative risk estimate to be used from each study is addressed in Section 5.2.1. In Section 5.2.2, each chosen relative risk estimate is adjusted downward to account for bias expected from some smokers misrepresenting themselves as nonsmokers. This topic has been a contentious issue in the literature for several years, with claims that this one source of systematic upward bias may account entirely for the excess risk observed in epidemiologic studies. Recent detailed investigation of this topic by Wells and Stewart (unpublished) make that claim unlikely (Appendix B). They found that a reasonable correction for bias, calculated on a study-by-study basis, is positive but small. Following this methodology, this report makes reductions in the relative risk estimates at the outset for each study individually before statistical inference or pooling estimates from studies of the same country. This is in contrast to the NRC report (1986), which makes the same downward adjustment to all studies (applied to an overall estimate of relative risk obtained after pooling all study estimates).

The estimates adjusted for smoker misclassification bias are the basis for statistical inference in Sections 5.3 (without regard to tier classification) and 5.5 (analysis by tier classification). Section 5.4 reviews the study results on potential modifying factors. Conclusions are then drawn for hazard identification (i.e., whether ETS is causally associated with increased lung cancer mortality) based on the total weight of evidence. Chapter 6 of this report addresses the upward adjustment on the U.S. relative risk estimate for background ETS exposures and the U.S. population risk of lung cancer from ETS.

5.2. RELATIVE RISKS USED IN STATISTICAL INFERENCE

5.2.1. Selection of Relative Risks

Two considerations largely affect the choice of relative risk (RR): (1) whether other relevant cofactors are taken into account (namely, potential confounders and risk modifiers that may be correlated with ETS exposure), and (2) the source and place of ETS exposure used. The alternatives (not yet adjusted for smoker misclassification) are shown by study in Tables 5-5 and 5-6, with the ones selected for analysis in this report in boldface type. Table 5-5 lists the RRs and their confidence intervals, along with explanatory footnotes, and Table 5-6 provides information on source and place of exposure and on the adjusted analysis. Because most studies include spousal smoking, and interstudy comparisons may be useful, spousal smoking was the preferred ETS surrogate in all except for LAMW and SOBU. In LAMW, spousal smoking data are limited to cases with adenocarcinoma; in SOBU, the data for cohabitants are separate from data for spousal smoking, and much of the ETS exposure appears to result from the cohabitants. Only data for broader exposure to ETS than spousal smoking alone were collected in BUFF, CHAN, SVEN, and HOLE(Coh).

Table 5-5. Estimated relative risk of lung cancer from spousal ETS by epidemiologic study (crude and adjusted for cofactors)

	Never-smokers	
Case-control	Crude RR[1,2]	Adj. RR[1,2,3]
AKIB	1.52 (0.96, 2.41)	1.5 (1.0, 2.5)
BROW	1.52[4] (0.49, 4.79) 1.82[4,5] (0.45, 7.36)[6]	* 1.68[4,5] (0.39, 6.90)[6]
BUFF	0.81[7] (0.39, 1.66)	*
CHAN	0.75[5] (0.48, 1.19)	*
CORR	2.07[8] (0.94, 4.52)	*
FONT[9]	1.37 (1.10, 1.69) 1.21 (0.94, 1.56) 1.32 (1.08, 1.61)	1.29 (1.03, 1.62) 1.28 (0.98, 1.66) *
GAO	1.19 (0.87, 1.63)	1.34[10,11]
GARF	1.31 (0.93, 1.85)	1.70[12] (0.98, 2.94)[6]
GENG	2.16 (1.21, 3.84)	*
HIRA[13]	1.53[10] (1.10, 2.13)	1.64[10] *
HUMB	2.34 (0.96, 5.69)	2.2 (0.9, 5.5)
INOU	2.55[14] (0.90, 7.20)	2.54[10,15] *
JANE	0.86 (0.57, 1.29)	0.93/0.44[16]

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Table 5-5. (continued)

Case-control	Never-smokers	
	Crude RR[1,2]	Adj. RR[1,2,3]
KABA[17]	0.79 (0.30, 2.04)	*
KALA	1.62[18] (0.99, 2.65) 1.41 (0.78, 2.55)	1.92 (1.02, 3.59)[6] *
KATA	*[19]	*
KOO	1.55 (0.98, 2.44)	1.64
LAMT	1.65 (1.22, 2.22)	*
LAMW	2.51[20] (1.49, 4.23)	*
LEE	1.03 (0.48, 2.20)	0.75/1.60[21]
LIU	0.74 (0.37, 1.48)	0.77 (0.35, 1.68)
PERS	1.28 (0.82, 1.98)	1.2 (0.7, 2.1)[6]
SHIM	1.08[22] (0.70, 1.68)	*
SOBU	1.06[18] (0.79, 1.44) 1.77 (1.29, 2.43)	1.13[18] (0.78, 1.63)[6] 1.57 (1.07, 2.31)[6]
SVEN	1.26[5] (0.65, 2.48)	1.4[5]
TRIC	2.08[23] (1.31, 3.29)	*
WU	1.41[24] (0.63, 3.15)	1.2 (0.6, 2.5)[6]
WUWI	0.79 (0.64, 0.98)	0.7

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Table 5-5. (continued)

Case-control	Never-smokers	
	Crude RR[1,2]	Adj. RR[1,2,3]
BUTL(Coh)	2.45[25]	**2.02 (0.48, 8.56)[6]**
GARF(Coh)	*	**1.17[10] (0.85, 1.61)[6]**
HIRA(Coh)	**1.38 (1.03, 1.87)**	1.61 *
HOLE(Coh)[26]	2.27 (0.40, 12.7)	**1.99 (0.24, 16.7)[6]**

[1]Parentheses contain 90% confidence limits, unless noted otherwise. When not represented in the original studies, the crude ORs and their confidence limits were calculated (or verified) by the reviewers wherever possible. Boldface indicates values used for analysis in text of this report. Odds ratios are shown for case-control studies; relative risks are shown for cohort studies.
[2]ORs for never-smokers apply to exposure from spousal smoking, unless indicated otherwise.
[3]Calculated by a statistical method that adjusts for other factors (see Table 5-3), but not corrected for smoker misclassification.
[4]Adenocarcinoma only. Data for crude OR values communicated from author (Brownson).
[5]Exposure at home and/or at work.
[6]95% confidence interval.
[7]Exposure to regularly smoking household member(s). Differs slightly from published value of 0.78, wherein 0.5 was added to all exposure cells.
[8]Excludes bronchioalveolar carcinoma. Crude OR with bronchioalveolar carcinoma included is reported to be 1.77, but raw data for calculation of confidence interval are not provided.
[9]The first, second, and third entries are calculated for population controls, colon cancer controls, and both control groups combined, respectively. For adenocarcinoma alone, the corresponding ORs, both crude and adjusted, are higher by 0.15-0.18.
[10]Composite measure formed from categorical data at different exposure levels.
[11]For GAO, data are given as (number of years lived with a smoker, adjusted odds ratio [OR]): (<20, 1.0), (20-29, 1.1), (30-39, 1.3), (40+, 1.7).
[12]Estimate for husband smoking 20 cig./day.
[13]Case-control study nested in the cohort study of Hirayama. OR for ever-smokers is taken from cohort study. This case-control study is not counted in any summary results where HIRA(Coh) is included.
[14]OR reported in study is 2.25, in contrast to the value shown that was reconstructed from the confidence intervals reported in the study; no reply to inquiry addressed to author had been received by press time.
[15]For INOU, data are given as (number of cig./day smoked by husband, adj. OR): (<19, 1.58), (20+, 3.09).
[16]From subject responses/from proxy responses.

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Table 5-5. (continued)

[17]For second KABA study (see addendum in study description of KABA in Appendix A), preliminary unpublished data and analysis based on ETS exposure in adulthood indicate 68% of never-smokers are exposed and OR = 0.90 (90% C.I. = 0.51, 1.58), not dissimilar from the table entry shown.

[18]For the first value, "ETS-exposed" means the spouse smokes; for the second value, "ETS-exposed" means a member of the household other than the spouse smokes.

[19]OR is not defined because number of unexposed subjects is zero for cases or controls.

[20]Table entry is for exposure to smoking spouse, cohabitants, and/or coworkers; includes lung cancers of all cell types. OR for spousal smoking alone is for adenocarcinoma only: 2.01 (90% C.I. = 1.20, 3.37).

[21]From subject responses/from spouse responses.

[22]From crude data, estimated to be: exposed cases 52, exposed controls 91, unexposed cases 38, unexposed controls 72.

[23]Known adenocarcinomas and alveolar carcinomas were excluded, but histological diagnosis was not available for many cases. Data are from Trichopoulos et al. (1983).

[24]Raw data for WU are from Table 11 of Surgeon General's report (U.S. DHHS, 1986). Data apply to adenocarcinoma only.

[25]RR is based on person-years of exposure to spousal smoking. "Prevalence" in those units is 20%.

[26]RR values under never-smoker are for lung cancer mortality. For lung cancer incidence, crude RR is 1.51 (90% C.I. = 0.41, 5.48) and adjusted RR is 1.39 (95% C.I. = 0.29, 6.61).

*Data not available.

Table 5-6. Effect of statistical adjustments for cofactors on risk estimates for passive smoking[1]

Case-control study	Exposure		Crude RR[4]	Adj. RR[4]	Adjustment factor(s)[5]	Adj. technique[6]
	Source[2]	Place[3]				
AKIB	Sp	A	1.52	1.5	A,L,O,V	LR
BROW	Sp	A	1.52	*	*	*
	A	P	1.82	1.68	A,I,O	LR
BUFF	Co	H	0.81	*	*	*
CHAN	A	A	0.75	*	*	*
CORR	Sp	A	2.07[7]	*	*	*
	M(C)	A	1.66[7]	1.36[7]	Sm	R
FONT	Sp	A	1.37[8]	1.29[8]	A,E,I,L,R	LR
	Sp	A	1.21[9]	1.28[9]	A,E,I,L,R	LR
GAO	Sp	A	1.19	1.34[10]	A,E	R
	A	A	*	0.9	A	LR
GARF	Sp	H	1.31	1.70	A,SES,H,Yd	R
GENG	Sp	A	2.16	*	*	*
HIRA	Sp	A	1.53[10]	1.64[10]	A,F,Oh,	S
	Sp	A	1.53	1.50	F	S
HUMB	Sp	A	2.34	2.2	A,R	R
INOU	Sp	A	2.55	2.54[10]	A	S
JANE	Sp	A	0.86	0.93/0.44[11]	A,L,R	M,S
	A(C)	H	*	1.09/2.07[12]	A,R	
KABA	Sp	A	0.79	*	*	*
KALA	Sp	A	1.62	1.92	A,E,Ir	LR
	OC	H	1.41	*	*	*
KOO	Sp	A	1.55	1.64	A,E,B,Yc	LR
	Co	H	1.34	1.68	A,E,B,Yc	LR
LAMT	Sp	A	1.65	*	*	*

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Table 5-6. (continued)

Case-control study	Exposure		Crude RR[4]	Adj. RR[4]	Adjustment factor(s)[5]	Adj. technique[6]
	Source[2]	Place[3]				
LAMW	Sp	*	2.01[13]	*	*	*
	A	*	**2.51**[14]	*	*	*
LEE	Sp	A	1.3[15]	1.60[15]	A	S
			0.75	0.75		
			[1.03	1.00]		
	Co	H	0.80	0.87[10]	A	S
LIU	Co	A	0.74	**0.77**	C	LR
PERS	Sp	A	1.28	**1.2**	A,V	M
	Sp	A	1.28	1.47[10]	A	S
SHIM	Sp	H	**1.08**	*	*	*
SOBU	Sp	A	1.06	1.13	A,E	S
	OC	A	1.77	**1.57**	A,E	S
SVEN	A	H,W	1.1/1.8[16]	1.2/2.1[16]	A	S
			(1.26)	(1.4)		
TRIC	Sp	A	**2.08**	*	*	*
WU	Sp	A	**1.41**[17]	1.2	A,L	M
					As	LR
WUWI	Sp	P	**0.79**	0.7	A,E,L	LR
	Co	P	0.78	0.7	A,E,L	LR
BUTL (Coh)	Sp	A	2.45	**2.02**	A	S
GARF (Coh)	Sp	A	*	1.27/1.10[18]	A	S
				1.17	A,E,L,R,Oh	S
				1.37/1.04[18]		
HIRA (Coh)	Sp	A	**1.38**	1.61	Ah	S
HOLE (Coh)	Co	A	2.27	**1.99**	A,SES	S

[1]Values used for inference in this report are shown in boldface.
[2]Source: A = anyone; (C) = childhood; Co = cohabitant(s); M = mother; OC = cohabitant(s) other than spouse; Sp = spouse.
[3]Place: A = anywhere; H = home/household; P = proximity of subjects; W = workplace.
[4]OR for case-control studies; RR for cohort studies.

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Table 5-6. (continued)

[5]Adjustment factors: A = age of subject; Ah = age of husband; As = age started smoking; B = number of live births; C = cooking habits; E = education; F = fish consumption; H = hospital; I = income; Ir = interviewer; L = location; O = occupation of subject; Oh = occupation of husband; R = racial or ethnic group; SES = socioeconomic status; Sm = active smoking; V = vital status; Yc = years since exposure ceased; Yd = year of diagnosis.
[6]LR = logistic regression; R = regression; M = matched analysis; S = stratified.
[7]Bronchioalveolar carcinoma excluded. Spousal smoking OR = 1.77 with bronchioalveolar carcinoma excluded; no corresponding value reported for maternal smoking.
[8]Population controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.52 and 1.47, respectively).
[9]Colon cancer controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.35 and 1.44, respectively).
[10]Composite measure formed from categorical data at different exposure levels.
[11]Cases and controls matched on A, L, and N; first value is from subject; second value is from proxy sources.
[12]1-24 smoker-years/$\geq$ 25 smoker-years.
[13]Adenocarcinoma only.
[14]All cell types.
[15]First value is for smoking information provided by patient's spouse; second value is for information provided by patient herself; third value (in brackets) utilizes available data from either source with subject classified as exposed if either source so indicates.
[16]Exposed at home but not at work or vice versa/exposed both at home and at work followed by weighted average of exposed strata.
[17]Crude OR from Table 11 of Surgeon General's report (U.S. DHHS 1986); note that adjusted OR from WU is not restricted to never-smokers and analysis includes only adenocarcinoma.
[18]Spouse smokes 1-20 cig. per day/spouse smokes $\geq$ 20 cig. per day. The composite RR is 1.17.

*Data not available.

After exposure source and place are taken into account in the choice of RR values in Table 5-6, an adjusted RR is considered preferable to a crude RR unless the study review in Section A.4 indicates a problem with the adjustment procedure. Of the 31 studies, 20 provide both an adjusted and crude RR, where the "adjusted estimate" is based on the author's use of a statistical procedure that takes potential confounding factors into account, usually by stratification or logistic regression. Based on the decision rule just described, our choice of RR is the smaller of the crude and adjusted values in 14 of the 20 studies providing both estimates. In several studies, RR values in addition to those shown in Table 5-6 might be considered (see Table 5-7). They were not found to be the best choices, however, for comparison between studies.

5.2.2. Downward Adjustment to Relative Risk for Smoker Misclassification Bias

There is ample evidence that some percentage of smokers, which differs for current and former smokers, misrepresent themselves as never-smokers (sometimes the wording of a

Table 5-7. Alternative estimates of lung cancer relative risks associated with active and passive smoking

Study	Active/ passive	ETS exposure	Controls exp. (%)	Alternative estimate	Comparison estimate[1]
BUFF[2]	Passive	Household members regularly smoking for 33+ years	71	Crude OR 0.95 (0.38, 2.40)	0.81
FONT[3]	Passive	Spousal smoking, all types	63	Crude OR 1.52[4] (1.19, 1.96)	1.37
				Adj. OR 1.47	1.29
			66	Crude OR 1.35[5] (1.02, 1.80)	1.21
				Adj. OR 1.44	1.28
			64	Crude OR 1.47[6] (1.15, 1.87)	1.32
				No adj. OR	*
HUMB[7]	Passive	Spousal cigarette smoking[7]	57	Crude OR 1.8 (0.6, 5.4)	2.3
				adj. OR 1.7	2.2
KOO[8]	Passive	Home and/or workplace exposure over lifetime[8]	64	Crude OR 1.36 (0.83, 2.21)	1.34
				Adj. OR 1.86	1.64
PERS[9]	Active	N.A.[10]	37[11]	Crude OR 4.2	*
SHIM[12]	Passive	Total household ETS exposure[12]	77	Crude OR 1.36	1.08
BUTL (Coh)	Active	N.A.[10]	14[11]	Adj. RR 4.0[13]	*
HIRA[14] (Coh)	Active	N.A.[10]	44[11]	Adj. RR 3.79	2.67
HOLE[15] (Coh)	Active	N.A.[10]	56[11]	Adj. RR 4.2	*

[1]Nearest equivalent from Tables 5-5 or 5-6.
[2]Values in Tables 5-5 and 5-6 include household smoking for any duration. Lung cancer may have a long latency period, however, so the extended exposure may be of interest.
[3]As in Table 5-5 except for adenocarcinoma alone.
[4]Population controls only.
[5]Colon cancer controls only.
[6]Control groups combined.
[7]Values in Tables 5-5 and 5-6 include spousal smoking of cigars and pipes.
[8]Value in Table 5-6 is for household cohabitant smoke exposure during adulthood.

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Table 5-7. (continued)

[9]Estimate is based on papers by Cederlöf et al. (1975) and Floderus et al. (1988) describing larger populations on which Pershagen study was based.
[10]Not applicable because alternative estimate is for active smoking.
[11]Percentage ever-smokers.
[12]Composite estimate from crude ORs for exposure from husband, parents, and father-in-law. Values in Tables 5-5 and 5-6 consider only spousal smoke exposure.
[13]Rough estimate based on data in Fraser et al. (1991). The prevalence of female ever-smoking is estimated from KALA and TRIC studies, which were conducted in similar conservative societies.
[14]Compares active smokers with never-smokers unexposed to ETS, thus providing a reference group more truly unexposed to tobacco smoke. The value in Table 5-5 is the more conventional comparison of ever-smokers with never-smokers, regardless of passive smoking status.
[15]Estimate is from adjusted RR for both sexes combined with assumption that female RR is 75% of male RR.

*Data not available.

questionnaire may not be explicit enough to distinguish former smokers from never-smokers) (see Appendix B). It has been argued that the resultant misclassification of some smokers as nonsmokers produces an upward bias in the observed relative risk for lung cancer from ETS exposure (i.e., the observed RR is too large). The essence of the supporting argument is based on smoking concordance between husband and wife--a smoker is more likely than a nonsmoker to have been married to a smoker. Consequently, the smoker misclassified as a nonsmoker is more likely to be in the ETS-exposed classification as well. Because smoking causes lung cancer, a misclassified smoker has a greater chance of being a lung cancer case than a nonsmoker. The net effect is that an observed association between ETS exposure and lung cancer among people who claim to be never-smokers may be partially explainable by current or former active smoking by some subjects.

The potential for bias due to misreported smoking habits appears to have been noted first by Lee (see discussion in Lehnert, 1984), and he emphasizes it in several articles (e.g., Lee, 1986, 1987a,b). In Lee, 1987b, it is argued that smoker misclassification may explain the entire excess lung cancer risk observed in self-reported never-smokers in epidemiologic studies. Lee's estimates of bias due to smoker misclassification appear to be overstated, however, for reasons discussed in Appendix B.

The NRC report on ETS (1986) devotes considerable attention to the type of adjustment for smoker misclassification bias. It follows the construct of Wald and coworkers, as described in Wald et al., 1986; Wald was the author of this section in the 1986 NRC report. An illustrative diagram for the implicit true relative risk of lung cancer from exposure to ETS in women from

spousal smoking is shown in Figure 2 of Wald et al. (1986). A similar example is in Table 12-5 of the NRC report.

Both Lee's and Wald's work adjust an overall relative risk estimate, pooled over several studies, downward, rather than address each individual study, with its own peculiarities, separately. Furthermore, statistical analysis over the studies as a whole is conducted first, and then an adjustment is made to the overall relative risk estimate. The recent work of Wells and Stewart (Appendix B) on this subject makes an adjustment to each individual study separately. Consequently, the pertinent adjustment factors that vary by study and type of society can be tailored to each study and then applied to the observed data before any statistical analysis. The latter procedure is applied in this report.

The methodology to adjust for bias due to smoker misclassification and the details of its application to the ETS studies are provided in Appendix B. The results of the adjustment and estimate of bias are given in Table 5-8. In general, the biases are low in East Asia, or in any traditional society such as Greece, where female smoking prevalence is low and the female smoker risk is low. Some of the calculated biases are slightly less than unity when carried to three decimal places. This may result from the assumption in the calculations that there is no passive smoking effect on current smokers.

5.3. STATISTICAL INFERENCE

5.3.1. Introduction

Table 5-9 lists the values of several statistical measures for the effect of spousal smoking by study (see boldface entries in Table 5-6 for details). Their meanings will be described before proceeding to interpretation of the data, even though the concepts discussed may be familiar to most readers. The p-values refer to a test for effect and a test for trend. In the former, the null hypothesis of no association (referred to as "no effect" of ETS exposure on lung cancer risk) is tested against the alternative of a positive association. The test for trend applies to a null hypothesis of no association between RR and exposure level against the alternative of a positive association. When data are available on more than two levels of intensity or duration of ETS exposure, typically in terms of the husband's smoking habit (e.g., cig./day or years of smoking), then a test for trend is a useful supplement in testing for an effect, as well as indicating whether a dose-response relationship is likely.

The entries under "power" in Table 5-9 are calculated for the study's ability to detect a true relative risk of 1.5 and a decision rule to reject the null hypothesis of no effect when $p < 0.05$ (see Dupont and Plummer [1990] for methods to calculate power). The power is the estimated probability that the null hypothesis would be rejected if the true relative risk is 1.5 (i.e., that the

Table 5-8. Estimated correction for smoker misclassification

Case control	Never-smokers RR[1] Uncorrected[2] (1)		Corrected[3] (2)	Bias[4] (1)/(2)	Ever-smokers OR used[5]
AKIB	———	1.5 (1.0, 2.5)	———	1.00	2.38
BROW	1.52 (0.49, 4.79)		1.50 (0.48, 4.72)	1.01	4.30
BUFF	0.81 (0.39, 1.66)		0.68 (0.32, 1.41)	1.20	7.06
CHAN	0.75 (0.48, 1.19)		0.74 (0.47, 1.17)	1.01	3.48
CORR	2.07 (0.94, 4.52)		1.89 (0.85, 4.14)	1.10	12.40
FONT	1.29 (1.03, 1.62)		1.28 (1.03, 1.60)	1.01	8.0
GAO	———	1.19 (0.87, 1.63)	———	1.00	2.54
GARF	1.31 (0.93, 1.85)		1.27 (0.91, 1.79)	1.03	6.0
GENG	———	2.16 (1.21, 3.84)	———	1.00 (0.995)	2.77
HIRA	1.53 (1.10, 2.13)		1.52 (1.10, 2.12)	1.01	3.20
HUMB	2.2 (0.9, 5.5)		2.00 (0.83, 4.97)	1.10	16.3
INOU	———	2.55 (0.90, 7.20)	———	1.00 (0.996)	1.66
JANE	0.86 (0.57, 1.29)		0.79 (0.52, 1.17)	1.09	8.0
KABA	0.79 (0.30, 2.04)		0.73 (0.27, 1.89)	1.08	5.90
KALA	———	1.92 (1.13, 3.23)	———	1.00	3.32
KATA	*		*	*	*
KOO	1.55 (0.98, 2.44)		1.54 (0.98, 2.43)	1.01	2.77
LAMT	1.65 (1.21, 2.21)		1.64 (1.21, 2.21)	1.01	3.77

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Table 5-8. (continued)

Case control	Never-smokers RR[1] Uncorrected[2] (1)		Corrected[3] (2)	Bias[4] (1)/(2)	Ever-smokers OR used[5]
LAMW	_____	2.51 (1.49, 4.23)	_____	1.00 (0.996)	4.12
LEE	1.03 (0.48, 2.20)		1.01 (0.47, 2.15)	1.02	4.61
LIU	_____	0.77 (0.35, 1.68)	_____	1.00	*
PERS	1.2 (0.7, 2.1)[6]		1.17 (0.75, 1.87)	1.03	4.2
SHIM	1.08 (0.70, 1.68)		1.07 (0.7, 1.67)	1.01	2.8
SOBU	_____	1.57 (1.13, 2.15)	_____	1.00	2.81
SVEN	1.26 (0.65, 2.48)		1.20 (0.63, 2.36)	1.05	6.00
TRIC	_____	2.08 (1.31, 3.29)	_____	1.00	2.81
WU	1.41 (0.63, 3.15)		1.32 (0.59, 2.93)	1.07	4.38
WUWI	0.79 (0.64, 0.98)		0.78 (0.63, 0.96)	1.01	2.24
BUTL (Coh)	2.02[7] (0.48, 8.56)[6]		2.01 (0.61, 6.73)	1.00	4.0
GARF (Coh)	1.17[7] (0.85, 1.61)[6]		1.16 (0.89, 1.52)	1.01	3.58
HIRA (Coh)	1.38 (1.03, 1.87)		1.37 (1.02, 1.86)	1.01	3.20
HOLE (Coh)	1.99[7] (0.24, 16.7)[6]		1.97 (0.34, 11.67)	1.01	4.2

[1]OR for case-control studies; RR for cohort studies.
[2]Adjusted OR in Table 5-5 is used unless the confidence interval is unknown or the study review (Appendix A) is critical of the method(s) used.
[3]Corrected (2) (estimate and confidence interval) equals uncorrected (1) times ratio [(2)/(1)]. All corrected 95% confidence intervals have been converted to 90% confidence intervals.
[4]Values shown are the lower of (calculated ratio, 1). Calculated ratios less than 1 are shown in parentheses.
[5]The crude OR for ever-smokers in Table 5-5 is used in the calculations for the corrected value (Appendix B), when available. Ever-smoker ORs for GARF, JANE, PERS, and SHIM are approximated from the data of other studies for suitable location and time period. The ever-smoker ORs for BUTL(Coh) and (LEE) are based on data in Fraser et al. (1991) and Alderson et al. (1985), respectively.
[6]95% confidence interval.
[7]Adjusted RR value in Table 5-5.

Table 5-9. Statistical measures by individual study and pooled by country, corrected for smoker misclassification[1]

Location	Study	Relative weight[2] (%)	Power[3]	P-value Effect[4]	P-value Trend[5]	RR[6]	Confidence interval 90%
Greece	KALA	43	0.39	0.02	0.04	1.92	(1.13, 3.23)
Greece	TRIC	57	0.45	<0.01	<0.01	2.08	(1.31, 3.29)
Greece	**ALL**	**5**		**<0.01**		**2.01**	**(1.42, 2.84)**
HK	CHAN	20	0.43	>0.5	*	0.74	(0.47, 1.17)
HK	KOO	20	0.43	0.06	0.16	1.54	(0.98, 2.43)
HK	LAMT	45	0.73	<0.01	<0.01	1.64	(1.21, 2.21)
HK	LAMW	15	0.39	<0.01	*	2.51	(1.49, 4.23)
HK	**ALL**	**14**		**<0.01**		**1.48**	**(1.21, 1.81)**
Japan	AKIB	15	0.42	0.05	0.03	1.50	(1.00, 2.50)
Japan	HIRA (Coh)	35	0.75	0.04	<0.01	1.37	(1.02, 1.86)
Japan	INOU	3	0.17	0.07	<0.03	2.55	(0.90, 7.20)
Japan	SHIM	16	0.37[7]	0.38	*	1.07	(0.70, 1.67)
Japan	SOBU	30	0.66	0.01	*	1.57	(1.13, 2.15)
Japan	**ALL**	**19**		**<0.01**		**1.41**	**(1.18, 1.69)**
USA	BROW	1	0.15	0.28	*	1.50	(0.48, 4.72)
USA	BUFF	3	0.17	>0.5	*	0.68	(0.32, 1.41)
USA	BUTL (Coh)	1	0.18	0.17	*	2.01	(0.61, 6.73)
USA	CORR	3	0.22	0.10	0.01	1.89	(0.85, 4.14)
USA	FONT[8]	35	0.93	0.03	0.04	1.28	(1.03, 1.60)
USA	GARF	15	0.60[7]	0.12	<0.02	1.27	(0.91, 1.79)

(continued on the following page)

Table 5-9. (continued)

Location	Study	Relative weight[2] (%)	Power[3]	P-value Effect[4]	P-value Trend[5]	RR[6]	Confidence interval 90%
USA	GARF (Coh)	25	0.92	0.18	*	1.16	(0.89, 1.52)
USA	HUMB	2	0.20	0.10	*	2.00	(0.83, 4.97)
USA	JANE	10	0.44[7]	>0.5	*	0.79	(0.52, 1.17)
USA	KABA	2	0.17[7]	>0.5	*	0.73	(0.27, 1.89)
USA	WU	3	0.21	0.29	*	1.32	(0.59, 2.93)
USA	**ALL**	**34**		**0.02**		**1.19**	**(1.04, 1.35)**
Scotland	HOLE (Coh)	100	0.09	0.26	*	1.97	(0.34, 11.67)
Eng./Wales	LEE	100	0.20	0.50	*	1.01	(0.47, 2.15)
Sweden	PERS	68	0.45[7]	0.27	0.12	1.17	(0.75, 1.87)
Sweden	SVEN	32	0.24	0.31	*	1.20	(0.63, 2.36)
W. Europe	**ALL**	**5**		**0.22**		**1.17**	**(0.84, 1.62)**
China	GAO	28	0.66	0.18	0.29	1.19	(0.87, 1.62)
China	GENG	8	0.32	0.01	<0.05	2.16	(1.21, 3.84)
China	LIU	4	0.18	>0.5	*	0.77	(0.35, 1.68)
China	WUWI	60	0.89[7]	>0.5	*	0.78	(0.63, 0.96)
China	**ALL**	**22**		**>0.5**		**0.95**	**(0.81, 1.12)**

[1]Misclassification is discussed in Section 5.2.2 and Appendix B.
[2]A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage).
[3]*A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4]One-sided p-value for test of RR = 1 versus RR > 1.
[5]P-value for upward trend. P-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative, i.e., upward trend.
[6]Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[7]Calculated for matched study design.
[8]For population control group only, all cases.

*Data not available; ns = not significant.

correct decision would result; the power would be larger if the true relative risk exceeds 1.5). If the estimates of power for the U.S. studies in Table 5-9 are used for illustration, it can be seen that the estimated probability that a study would *fail* to detect a true relative risk of 1.5 (equal to 1 – Power, the probability of a Type II error [discussed in the next paragraph] when the true relative risk is 1.5) is as follows: FONT, 0.07; GARF(Coh), 0.08; GARF, 0.40; JANE, 0.56; BUFF, 0.83; CORR, 0.78; WU, 0.79; HUMB, 0.80; KABA, 0.83; BUTL(Coh), 0.82; and BROW, 0.85. Thus, 7 of the 11 U.S. studies have only about a 20% chance of detecting a true relative risk as low as 1.5 when taken alone. Sources of bias effectively alter the power in the same direction as the bias (e.g., a downward bias in RR decreases the power). Of the potential sources of bias discussed by study in Section A.4, the predominant direction of influence on the observed RR, when identifiable, appears to be in the direction of unity, thus affecting power adversely. The RRs already have been reduced to adjust for smoker misclassification, the only systematic source of upward bias that has been established.

Studies of all sizes, large and small, are equally likely to make a false conclusion if ETS is not associated with lung cancer risk (Type I error). However, smaller studies are less likely to detect a real association when there is one (Type II error). This imbalance comes from using the significance level of the test statistic to determine whether to reject the null hypothesis. If the decision rule is to reject the hypothesis when the p-value is smaller than some prescribed value (e.g., 0.05), then the Type I error rate is 0.05, but the Type II error rate increases as study size decreases. When a study with low power fails to reject the null hypothesis of no effect, it is not very informative because that outcome may be nearly as likely when the null hypothesis is false as when it is true. When detection of a small relative risk is consequential, pooling informational content of suitably chosen studies empowers the application of statistical methods.

The heading in Table 5-9 that remains to be addressed is "relative weight," to be referred to simply as "weight." When the estimates of relative risk from selected studies are combined, as for studies within the same country as shown in the table, the logarithms of the RRs are weighted inversely proportional to their variances (see Appendix D and footnote 2 of Table 5-9). These relative weights are expressed as percentages summing to 100 for each country in Table 5-9. Study weight and power are positively associated, which is explained by the significant role of study size to both. Consequently, studies weighted most heavily (because the standard errors of the RRs are low) also tend to be the ones with the highest power (most likely to detect an effect when present).

5.3.2. Analysis of Data by Study and Country

5.3.2.1. *Tests for Association*

The p-values of the test statistics for the hypothesis of no effect (i.e., RR = 1) are shown in Table 5-9. Values of the test statistics (the standardized log odds ratio; see Appendix D) are plotted in Figure 5-1. Also shown in Figure 5-1 for reference are the points on the horizontal axis corresponding to p-values of 0.5, 0.2, 0.1, 0.05, 0.01, and 0.001. For example, the area under the curve to the right of the vertical line labeled p = 0.01 is 0.01 (1%), so it is apparent from Figure 5-1 that three studies had significance levels $p < 0.01$ (more specifically, $0.001 < p < 0.01$). The size of the symbol (inverted triangle) used for a study is proportional in area to the relative weight of that individual study, but of current interest is the location and not the size of the symbol. If the null hypothesis is true, then the plotted values would arise from a standard normal distribution, shown in the figure (points to the left of zero indicate that the RR is less than 1, and points to the right of zero indicate that RR is greater than 1). If the points lie more toward the right side of the normal curve than would be likely to occur by chance alone, then the hypothesis of no effect is rejected in favor of a positive association between ETS exposure and lung cancer. If one constructs five intervals of equal probability (i.e., intervals of equal area under the standard normal curve), the expected number of observations in each interval is six (these five intervals are not shown on Figure 5-1). The observed numbers in these intervals, however, from left to right are 3, 3, 1, 7, and 16, an outcome that is significant at $p < 0.005$, by the chi-square goodness-of-fit test. At the points on the standard normal curve corresponding to p-values 0.5, 0.4, 0.3, 0.2, 0.1, and 0.05, the probability that a number of outcomes as large as that actually observed would occur by chance is less than 0.005 at all points. Consequently, the hypothesis of no effect is rejected on statistical grounds, and that conclusion is not attributable to a few extreme outcomes that might be aberrant in some way.

Figure 5-2 displays the U.S. studies alone (see Appendix D for calculation of the test statistics). Figure 5-3 corresponds to Figure 5-1 except that the test statistics for the hypothesis of no effect (i.e., RR = 1) for the significance levels shown apply to a single overall estimate of RR for each country, formed by statistically pooling the outcomes from the studies within each country. The areas of the symbols for countries are also in proportion to statistical weight as given in Table 5-9. It is implicitly assumed that studies within a country, and the subpopulations sampled, are sufficiently homogeneous to warrant combining their statistical results into a single estimate for the country (see Greenland [1987] for a discussion of applications of meta-analysis to epidemiology). The calculational method employed weights the observed RR from each study within a country inversely proportional to its estimated variance (see Appendix D). The relative

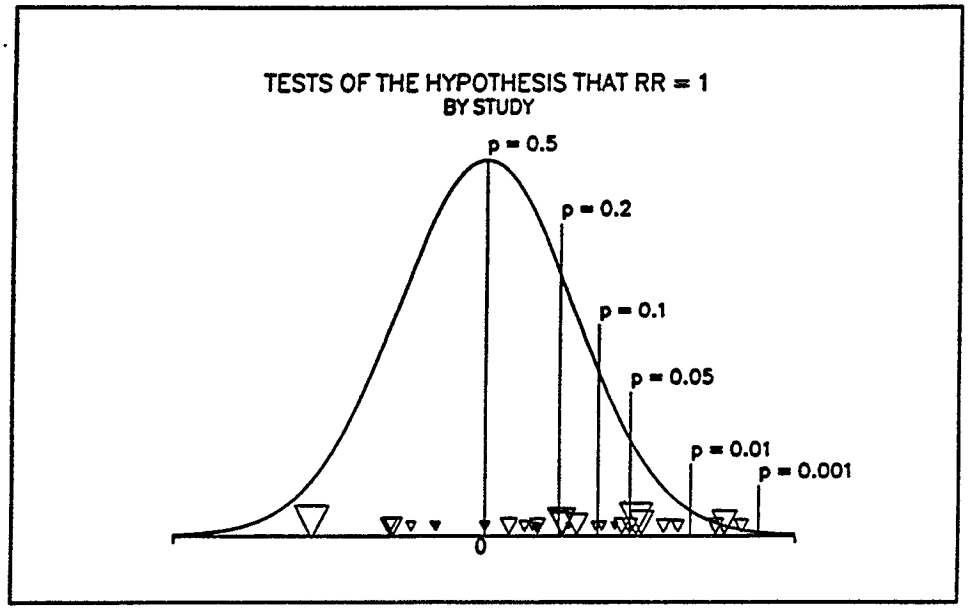

Figure 5-1. Test statistics for hypothesis RR = 1, all studies.

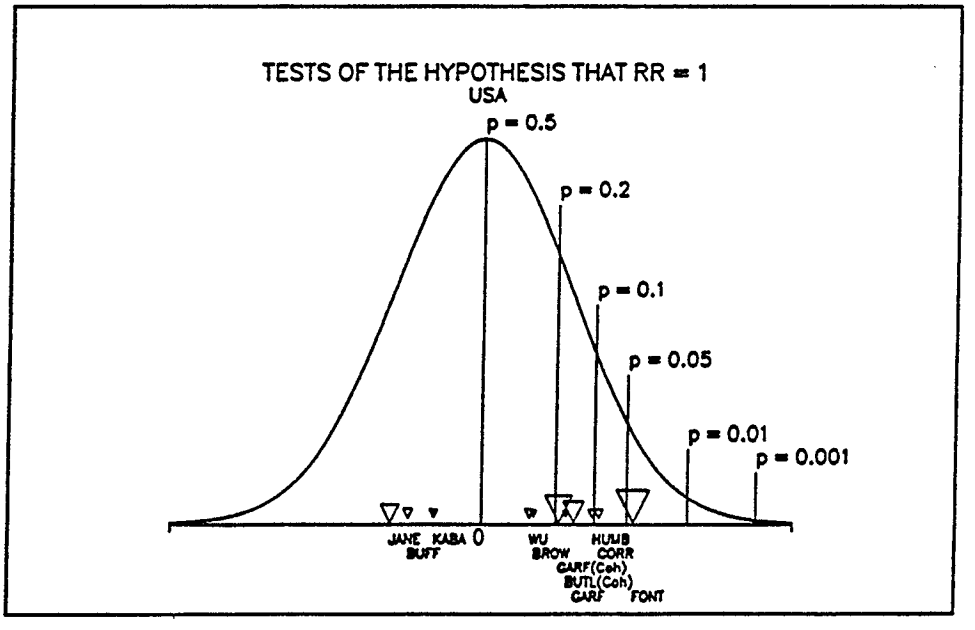

Figure 5-2. Test statistics for hypothesis RR = 1, USA only.

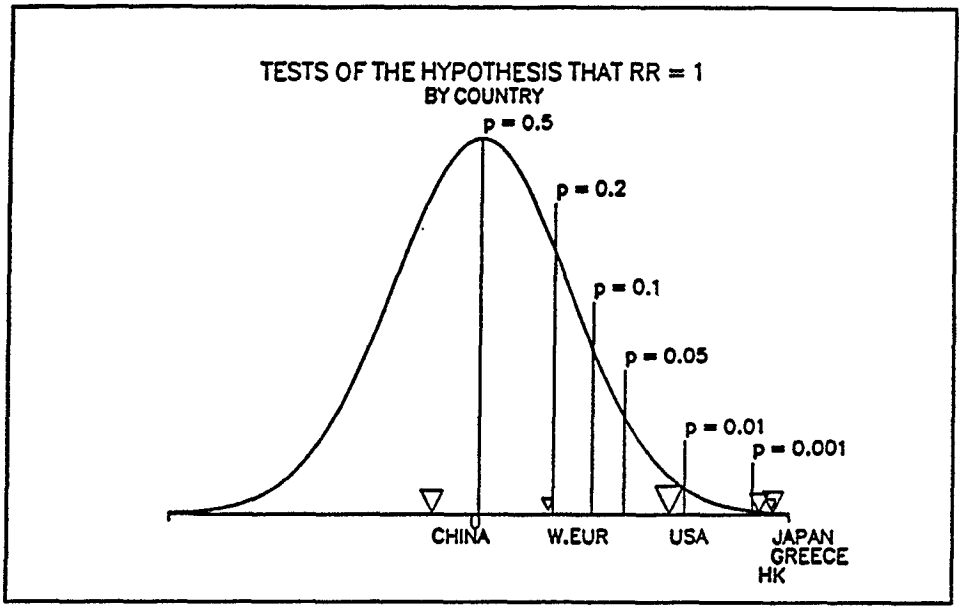

Figure 5-3. Test statistics for hypothesis RR = 1, by country.

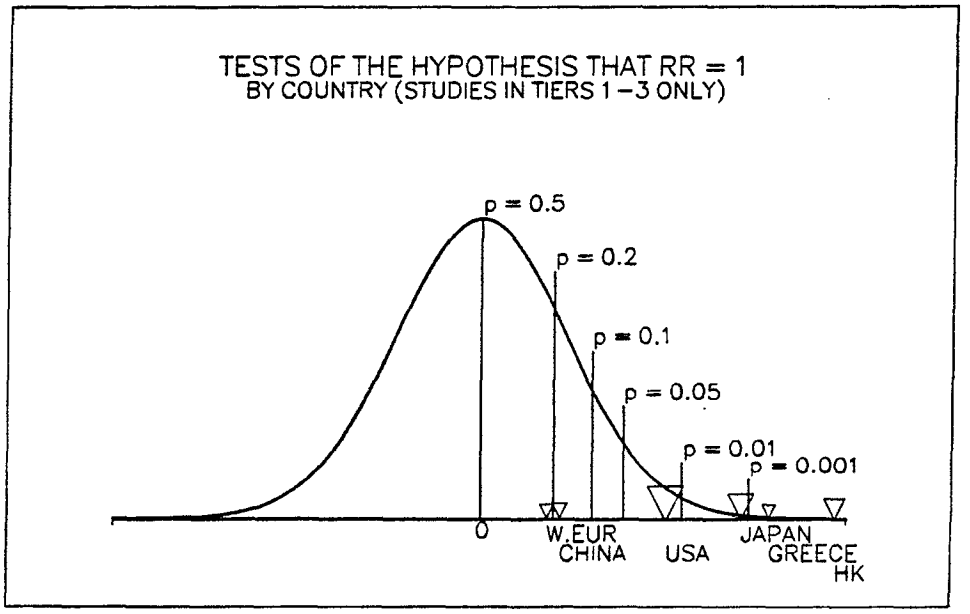

Figure 5-4. Test statistics for hypothesis RR = 1, tiers 1-3 only.

study weights are shown in Table 5-9. Each symbol in Figures 5-1, 5-2, 5-3, and 5-4 has been scaled so that its area is proportional to the weight of the outcome represented, relative to all other outcomes shown in the same figure.

Greece, Hong Kong, and Japan, which together comprise a total weight of 39%, are *each* statistically significant at $p < 0.01$ against the null hypothesis of no increase in relative risk ($RR = 1$). When the United States is included, the total weight is 73%, and *each* of the four countries is significant at $p < 0.02$. The four studies combined into the group called Western Europe are not large. Together they represent 5% of the total weight, and their combined odds ratio (1.17) is slightly above 1 but not statistically significant ($p = 0.21$). In contrast, China is weighted quite high (22%), the p-value is large (0.66), and the odds ratio is less than 1 (0.95), strongly indicating no evidence of an increase in RR due to ETS. This is largely because China is very heavily influenced by WUWI (relative weight of 60% of China), which is a very large case-control study. However, this apparent inconsistency in WUWI may be due to the presence of indoor smoke from cooking and heating, which may mask any effect from passive smoking. A similar but more extreme situation is found in LIU, conducted in a locale where indoor heating with smoky coal (an established risk factor for lung cancer) and inadequate venting are common. Both WUWI and LIU were conducted primarily to assess the hazardous potential of these pollutants. The indoor environments of the populations sampled in WUWI and LIU make detection of any carcinogenic hazard from ETS unlikely, and thus render these studies to be of little value for that purpose (see discussions of WUWI and LIU in Section A.4). Without WUWI or LIU, the combined results of the two remaining studies in China, GAO and GENG, are significant at $p = 0.03$.

Such qualitative considerations about the likely utility of a study to detect an ETS effect, if one exists, are taken into account in Section 5.5. In that section, studies are ranked into one of four tiers based on their likely utility. Studies such as WUWI and LIU would be placed into Tier 4, the grouping with the least likelihood of providing useful information on the effects of ETS. Figure 5-4 is similar to Figure 5-3 displaying the distribution of test statistics for the pooled estimates by country, but includes only the studies in Tiers 1, 2, and 3; it is shown here for comparison purposes (see Section 5.5 for a detailed discussion of the analysis based on tiers).

5.3.2.2. *Confidence Intervals*

Confidence intervals for relative risk are displayed by study and by country in Table 5-9 (see Appendix D for method of calculation). The 90% confidence intervals by country are illustrated in Figure 5-5. (*Note*: 90% confidence intervals are used for correspondence to a right-

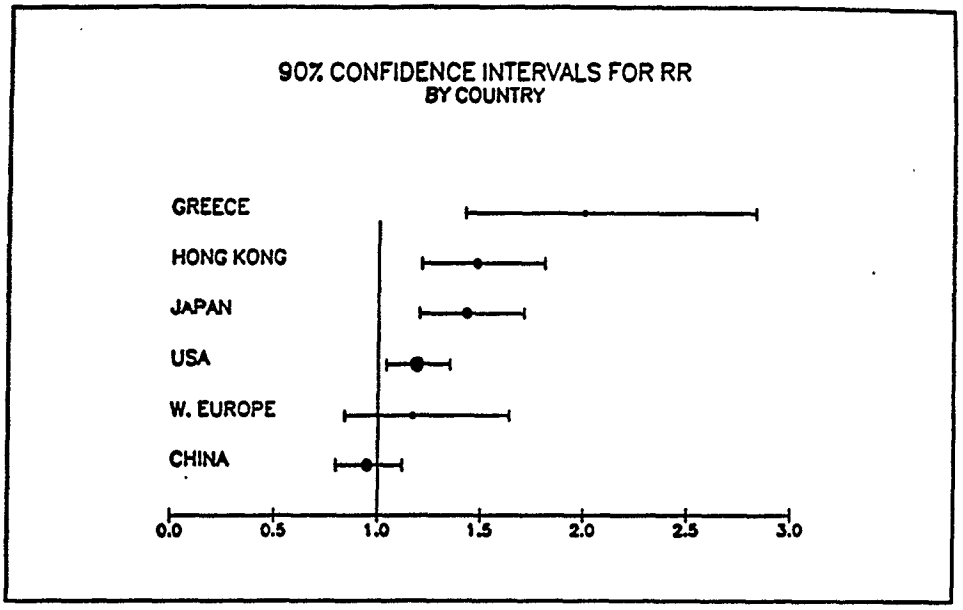

Figure 5-5. 90% confidence intervals, by country.

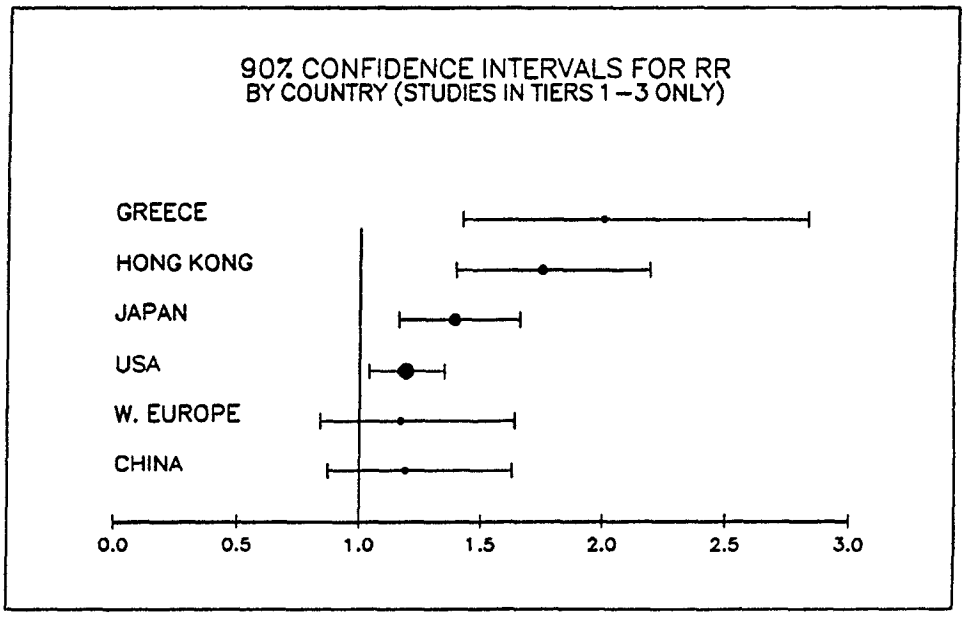

Figure 5-6. 90% confidence intervals, by country, tiers 1-3 only.

tailed test of the hypothesis of no effect at a 5% level of significance.) The area of the symbol (solid circle) locating the point estimate of relative risk within the confidence interval is proportional to study weight. Symbol size is used as a device to draw attention to the shorter confidence intervals, which tend to be based on more data than the longer ones. The confidence intervals for countries jointly labeled as Western Europe are in Table 5-9, except for Sweden which contains two studies, PERS and SVEN. For those two studies combined, the odds ratio (OR) is 1.19 (90% C.I. = 0.81, 1.74). The confidence intervals for the pooled relative risk estimates by country for studies in Tiers 1, 2, and 3 only (see previous paragraph and Section 5.5) are displayed in Figure 5-6.

In descending order, the relative risks in Figure 5-6 are for Greece, Hong Kong, Japan, the United States, and Western Europe. (China is being excluded from this summary because it contains only one study in Tiers 1-3 [GAO], which is unlikely to be representative of such a vast country. The relative risk estimate for that study, 1.19, is similar to the overall relative risks for the United States and Western Europe.) The estimated relative risks from exposure to spousal smoking differ between countries, with Greece, Hong Kong, and Japan at the high end of the scale and the United States and Western Europe at the low end. These differences suggest that combining studies from different countries should be done with caution. The relative risks pertain only to ETS exposure from spousal smoking, which may be a higher proportion of total ETS exposure in some countries than in others. This also emphasizes the importance of taking into account exposure and background (nonspousal) ETS, which is considered in the estimation of population risk for the United States in Chapter 6.

5.3.3. Analysis of Data by Exposure Level

5.3.3.1. *Introduction*

In Section 5.3.2, analyses are conducted by individual study and by studies pooled within countries, using the dichotomous data on spousal smoking (i.e., any level of spousal smoking versus no spousal smoking) as a surrogate for ETS exposure. This section examines the response data from all of the studies that provide data analysis by exposure-level categories. Exposure level, for these studies, refers to the amount of spousal smoking. In different studies, exposure is measured by intensity (e.g., cig./day smoked by the husband), duration (e.g., number of years married to a smoker), or a combination of both (e.g., number of pack-years--packs per day × years of smoking by the husband). The data are analyzed by calculating RR estimates for the highest exposure groups only (Section 5.3.3.2) and then by testing for an upward trend in RR across exposure groups within studies as ETS exposure increases (Section 5.3.3.3).

An evaluation of the highest exposure group or a test for exposure-related trend may be able to detect an association that would be masked in a test for effect using only dichotomous data. This masking is especially likely to occur when dealing with a weak association or a crude surrogate measure for exposure that is widespread (i.e., greater potential for exposure misclassification), both of which are difficulties in studies of ETS and lung cancer.

As discussed in Chapter 3, ETS is a dilute mixture, and, consequently, any association observed between environmental levels of ETS exposure and lung cancer is likely to be weak (i.e., have a low RR). Furthermore, questionnaire-based assessment of exposure to ETS is a crude indicator of actual lifetime exposure, and spousal smoking is an incomplete surrogate for exposure because it does not consider ETS from other sources, such as the workplace. Therefore, exposure misclassification in both directions is inevitable. For example, there will be women whose husbands do not smoke but who are exposed to substantial levels of ETS from other sources, and there will be women whose husbands smoke but who are not actually exposed to appreciable levels of ETS. This latter scenario is most likely if the level of spousal smoking is low. Comparing the highest exposure group with the "unexposed" group will help reduce the effect of this latter type of exposure misclassification bias.

In addition, the detection of an exposure-response relationship (trend) across exposure groups increases support for a causal association by diminishing the likelihood that the results can be explained by confounding, because any potential confounder would have to be associated with both lung cancer and ETS exposure in a dose-related manner. However, the potential for exposure misclassification is compounded when the exposed group is further divided into level-of-exposure categories and the sample sizes become small. This is especially problematic in small studies. These inherent difficulties with the ETS database tend to diminish the possibility of detecting exposure-response relationships. Therefore, the inability to demonstrate an exposure-response trend is not considered evidence against causality; rather, if a statistically significant trend can be detected despite these potential obstacles, it provides evidential support for a causal association.

5.3.3.2. *Analysis of High-Exposure Data*

In this section, analyses will be conducted for the highest exposure groups by study and by studies pooled within countries. As described in Section 5.3.3.1, analyzing only the data from the highest exposure group of each study increases the sensitivity for detecting an association and reduces the effects of exposure misclassification. Fractionating the data, however, does decrease the power to observe statistical significance.

The results of statistical inference using only data from the highest exposure categories are displayed in Table 5-10. As indicated in the table, exposure-level data are available in 17 studies. The definitions of highest exposure category, shown next to the study name in the table, vary widely between studies. Crude RR estimates adjusted for smoker misclassification (see Section 5.2 and Appendix B) are used in this section rather than the estimates adjusted for modifying factors within the studies, because the latter are available by exposure level for only a limited number of studies.

Several observations are apparent from Table 5-10. First, every one of the 17 individual studies shows increased risk at the highest exposure level, even after adjusting for smoker misclassification. Second, 9 of the 16 comparisons for which sufficient data are available are statistically significant ($p \leq 0.05$), despite most having very low statistical power. Third, the RR estimates pooled within countries are each statistically significant with $p \leq 0.02$. Although the RR estimates within a country are pooled across different definitions of highest exposure, which somewhat limits their interpretation and practical value, it is apparent that these RRs are considerably higher than the values observed for the dichotomous data (Table 5-9). The RR estimates pooled by country vary from a low of 1.38 ($p = 0.005$) for the United States to a high of 3.11 ($p = 0.02$) for Western Europe, which contains only one study. Finally, the overall pooled estimate of 1.81 for the highest exposure groups from all 17 studies is highly statistically significant ($p < 0.000001$).

These results are consistent with the statistical evidence presented in Section 5.3.2 for an association between ETS exposure and lung cancer. In fact, increased risks are found for the highest exposure groups without exception. Furthermore, the RR estimates pooled within countries are all statistically significant and range from 1.38 to 3.11, even after adjustment for smoker misclassification. The consistency of these highest exposure results cannot be accounted for by chance, and the stronger associations detected for the highest exposure groups across all countries further reduce the likelihood that bias or confounding could explain the observed relationship between ETS and lung cancer.

In addition, with the exception of Western Europe, which contains only one low-power study in this analysis, the pooled RR estimates from other, more "traditional" countries are all appreciably higher than that from the United States. It is likely that these differences are at least partially a result of higher background (nonspousal) ETS exposures to the allegedly "unexposed" group in the United States. Again, this highlights the importance of accounting for ETS exposures from sources other than spousal smoking. An adjustment for background ETS exposures is made in Chapter 6, for the estimation of population risk for the United States.

Table 5-10. Statistical measures for highest exposure categories only[1]

Location	Study	Highest exposure level	Relative weight[2] (%)	Power[3]	P-value Effect[4]	RR[5,6]	Confidence interval[6] 90%
Greece	KALA	(≥41 cig./day)	35	0.06	0.16	1.57	(0.74, 3.32)
Greece	TRIC	(≥21 cig./day)	65	0.11	0.003	2.55	(1.46, 4.42)
Greece	All	High	8		0.002	2.15	(1.38, 3.35)
Hong Kong	KOO	(≥21 cig./day)	36	0.11	0.36	1.18	(0.58, 2.55)
Hong Kong	LAMT	(≥21 cig./day)	64	0.16	0.02	2.05	(1.18, 3.57)
Hong Kong	All	High	8		0.03	1.68	(1.08, 2.62)
Japan	AKIB	(≥30 cig./day)	6	0.10	0.13	2.1	(0.7, 2.5)
Japan	HIRA (Coh)	(≥20 cig./day)	89	0.13	0.00015	1.91	(1.42, 2.56)
Japan	INOU	(≥20 cig./day)	4	*	0.05	3.09	(1.0, 11.8)
Japan	All	High	22		<0.00004	1.96	(1.49, 2.60)
United States	CORR	(≥41 pack-yrs)	8	0.06	0.005	3.20	(1.53, 6.74)
United States	FONT	(≥80 pack-yrs)	14	*	0.21	1.32[7]	(0.75, 2.29)
United States	GARF	(≥20 cig./day)	15	0.21	0.01	2.05	(1.19, 3.49)
United States	GARF (Coh)	(≥20 cig./day)	45	*	0.33	1.09	(0.81, 1.49)
United States	HUMB	(≥21 cig./day)	2	*	0.46	1.09	(0.27, 4.73)
United States	JANE	(≥50 pack-yrs)	8	*	0.50	1.01	(0.50, 2.04)
United States	WU	(≥31 years)	8[8]	*	*	1.87	*
United States	All	High	36		0.005	1.38	(1.13, 1.70)
W. Europe	PERS	(≥16 cig./day)	100	*	0.02	3.11	(1.18, 7.71)
W. Europe	All	High	2		0.02	3.11	(1.18, 7.71)
China	GAO	(≥40 years)	35	0.33	0.02	1.7	(1.09, 2.65)
China	GENG	(≥20 cig./day)	65	*	<0.00001	2.76	(2.02, 3.84)
China	All	High	24		<0.000001	2.32	(1.78, 3.03)
All	All	High			<0.000001	1.81	(1.60, 2.05)

(continued on the following page)

Table 5-10. (continued)

[1]Similar to Table 5-9 except entries apply to highest exposure category only in each study. Only studies with data available for categorized measures of exposure are included. Relative risks and confidence bounds are corrected for smoker misclassification.
[2]A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage).
[3]*A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4]One-sided p-value for test of RR = 1 versus RR > 1.
[5]Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[6]Values may differ from those of Table 5-11, where confidence intervals are shown as they appear in the source. In Table 5-11, the RR and confidence interval are *not* corrected for smoker misclassification, as in this table, and most of the confidence intervals are 95% instead of 90%.
[7]Value shown is for all cell types with the two control groups combined. For adenocarcinoma cases only, the RR is 1.68 with C.I. = 0.81, 3.46.
[8]Relative weight assumed to be the same as for CORR, based on the outcome in Table 5-9.

*Data not available.

5.3.3.3. *Tests for Trend*

In this section, exposure-response data from the studies providing data by exposure level are tested for upward trend. An exposure-response relationship provides strong support for a causal association (see Section 5.3.3.1).

Table 5-11 presents the female exposure-response data and trend test results from the studies of ETS and lung cancer discussed in this report. The p-values reported in the table are for a test of no trend against the one-sided alternative of an upward trend (i.e., increasing RR with increasing exposure). (*Note*: The results for tests of trend are taken from the study reports. Unless the report specified that a one-sided alternative was used, the reported p-value was halved to reflect the outcome for the one-sided alternative of RR increasing with exposure. Where the data are available, the p-values reported by the individual study's authors have been verified here by application of the Mantel, Haenszel test [Mantel, 1963].)

Wu-Williams and Samet (1990) previously reviewed the exposure-response relationships from the epidemiologic studies on ETS then available. They determined that 12 of 15 studies were statistically significant for the trend test for at least one exposure measure. The probability of this proportion of statistically significant results occurring by chance in this number of studies is virtually zero ($p < 10^{-13}$). Intensity of spousal smoking was the most consistent index of ETS exposure for the demonstration of an exposure-response relationship.

Our assessment of the exposure-response data is similar and provides essentially the same results for a slightly different set of studies. Table 5-12 summarizes the p-values of the trend

Table 5-11. Exposure response trends for females

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
AKIB	21	82		1.0		0.03
(cig./day)	29	90	1-19	1.3	(0.7, 2.3)[5]	
	22	54	20-29	1.5	(0.8, 2.8)[5]	
	12	23	≥30	2.1	(0.7, 2.5)[5]	
AKIB	21	82	0	1.0		0.24
(years)	20	30	1-9	2.1	(1.0, 4.3)[5]	
	29	81	20-39	1.5	(0.8, 2.7)[5]	
	22	59	≥40	1.3	(0.7, 2.5)[5]	
CORR	8	72	0	1.00		0.01
(pack-yrs.)	5	38	1-40	1.18	(0.44, 3.20)	
	9	23	≥41	3.52	(1.45, 8.59)	
FONT[6]	*	*	0	1.00		0.07
(years)	*	*	1-15	1.19	(0.88, 1.61)	
	*	*	16-30	1.14	(0.82, 1.59)	
	*	*	>30	1.25	(0.91, 1.72)	
FONT[7]	*	*	0	1.00		0.02
(years)	*	*	1-15	1.33	(0.93, 1.89)	
	*	*	16-30	1.40	(0.96, 2.05)	
	*	*	>30	1.43	(0.99, 2.09)	
FONT[6]	*	*		1.00		0.04
(pack-yrs.)	*	*	0<15	0.96	(0.72, 1.29)	
	*	*	15-39	1.13	(0.81, 1.59)	
	*	*	40-79	1.25	(0.86, 1.81)	
	*	*	≥80	1.33	(0.68, 2.58)	
FONT[7]	*	*		1.00		0.01
(pack-yrs.)	*	*	0<15	1.03	(0.73, 1.46)	
	*	*	15-39	1.26	(0.85, 1.87)	
	*	*	40-79	1.49	(0.98, 2.27)	
	*	*	≥80	1.70	(0.82, 3.49)	
GAO	99	57	0-19	1.0		0.29
(tot. yrs.)[8]	93	63	20-29	1.1	(0.7, 1.8)	
	107	78	30-39	1.3	(0.8, 2.1)	
	76	48	≥40	1.7	(1.0, 2.9)	
GARF	44	157	0	1.00		<0.02
(cig./day)	29	90	1-9	1.15	(0.8, 1.6)	
	17	56	10-19	1.08	(0.8, 1.5)	
	26	44	≥20	2.11	(1.1, 4.0)	
GENG	*	*	0	1.00		<0.05[9]
(cig./day)	*	*	1-9	1.40	(1.1, 1.8)	
	*	*	10-19	1.97	(1.4, 2.7)	
	*	*	≥20	2.76	(1.9, 4.1)	

(continued on the following page)

Table 5-11. (continued)

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
GENG	*	*	0	1.00		<0.05[9]
(years)	*	*	<20	1.49	(1.15, 1.94)	
	*	*	20-39	2.23	(1.54, 3.22)	
	*	*	≥40	3.32	(2.11, 5.22)	
HUMB	*	*	0	1.0		ns
(cig./day)	*	*	1-20	1.8	(0.6, 5.6)[5]	
	*	*	≥21	1.2	(0.3, 5.2)[5]	
INOU	*	*	0-4	1.00		<0.03
(cig./day)	*	*	5-19	1.58	(0.4, 5.7)[5]	
	*	*	≥20	3.09	(1.0, 11.8)[5]	
JANE[10]	*	*	0	1.00		*
(pack-yrs.)	*	*	1-24	0.71	(0.37, 1.35)	
	*	*	25-49	0.98	(0.47, 2.05)	
	*	*	≥50	1.10	(0.47, 2.56)	
KALA	26	46	0	1.00		0.08
(cig./day)	34	39	1-20	1.54	(0.88, 2.70)	
	22	22	21-40	1.77	(0.93, 3.35)	
	8	9	41+	1.57	(0.64, 3.85)	
KALA	26	46	0	1.00		0.04
(years)	15	21	<20	1.26	(0.56, 2.87)	
	15	20	20-29	1.33	(0.58, 3.03)	
	17	15	30-39	2.01	(0.86, 4.67)	
	17	16	≥40	1.88	(0.82, 4.33)	
KOO	32	67	0	1.00		0.16
(cig./day)	17	15	1-10	2.33	(0.9, 5.9)	
	25	35	11-20	1.74	(0.8, 3.8)	
	12	19	≥21	1.19	(0.5, 3.0)	
LAMT[6]	84	183	0	1.00		0.01
(cig./day)	22	22	1-10	2.18	(1.14, 4.15)	
	56	66	11-20	1.85	(1.19, 2.87)	
	20	21	≥21	2.07	(1.07, 4.03)	
LAMT[7]	53	92	0	1.00		0.01
(cig./day)	17	12	1-10	2.46	(1.09, 5.54)	
	37	28	11-20	2.29	(1.26, 4.16)	
	15	9	≥21	2.89	(1.18, 7.07)	

(continued on the following page)

Table 5-11. (continued)

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
PERS[11]	34	*	0	1.0		0.12
(cig./day)	26	*	1-15	1.0	(0.6, 1.8)	
	7	*	≥16	3.2	(1.0, 9.5)	
TRIC[12]	24	109	0	1.00		0.01
(cig./day)	24	56	1-20	1.95	(1.13, 3.36)	
	14	25	≥21	2.55	(1.31, 4.93)	
WU[13]	*	*	0	1.0		*
(years	*	*	1-30	1.2	*	
exposed as	*	*	≥31	2.0	*	
adult)						
GARF(Coh)[14]	65	*	0	1.00		*
	39	*	1-19	1.27	(0.85, 1.89)	
(cig./day)	49	*	≥20	1.10	(0.77, 1.61)	
HIRA(Coh)[15]	37	21,895	0	1.00		0.01
	99	44,184	1-19[16]	1.41	(1.03, 1.94)	
(cig./day)	64	25,461	≥20	1.93	(1.35, 2.74)	

[1]Smoking by spouse unless otherwise specified.
[2]See footnote 6 in Table 5-10.
[3]Confidence intervals are 95% unless noted otherwise.
[4]P-value for upward trend. P-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative (i.e., upward trend). Values below 0.01 are shown as 0.01.
[5]90% confidence interval.
[6]All histologies.
[7]Adenocarcinomas only.
[8]Years lived with a smoking husband.
[9]Neither crude data nor a test for trend is included in reference articles. The relative risk at each exposure category is significant alone, however, at $p < 0.05$.
[10]Data are from subject responses in Table 3 of the source.
[11]Low exposure level is for husband smoking up to 15 cigarettes per day or one pack (50 g) of pipe tobacco per week, or smoking any amount during less than 30 years of marriage. High exposure level is for husband smoking more than 15 cigarettes per day or one pack of pipe tobacco per week during 30 years of marriage or more.
[12]Data from Trichopoulos et al. (1983), with RRs corrected (personal communication from Trichopoulos, 1984).
[13]Years of exposure to spousal smoke *plus* years of exposure to workplace smoke; adenocarcinomas only.
[14]Value under "RR" is mortality ratio of observed to expected lung cancer deaths. Value under "Case" is number of observed lung cancer deaths.
[15]Standardized for age of subject (Hirayama, 1984). Values under "case" are numbers of lung cancer deaths; values under "cont." are total population.
[16]Includes former smokers of any exposure level.

*Data not available; ns = not significant.

Table 5-12. Reported p-values of trend tests for ETS exposure by study[1]

	Trend test results		
	Intensity (cig./day)	Duration (total years)	Cumulative (pack-years)[2]
AKIB	0.03	0.24	*
CORR	*	*	0.01
FONT	*	0.07[3]	0.04
	*	<0.02[4]	<0.01
GAO	*	0.29	*
GARF	<0.02	*	*
GENG	<0.05[5]	<0.05[5]	*
HUMB	ns	*	*
INOU	<0.03	*	*
JANE	*[6]	*	*
KALA	0.08	0.04	*
KOO	0.16	*	*
LAMT	<0.01	*	*
	<0.01[4]		
PERS	0.12	*	*
TRIC	<0.01	*	*
WU	*	*[6]	*
GARF(Coh)	*[6]	*	*
HIRA(Coh)	<0.01	*	*

[1]Detailed data presented in Table 5-11.
[2]A "pack-year" is equivalent to one pack/day for 1 year.
[3]All cell types.
[4]Adenocarcinoma only.
[5]See footnote 9 in Table 5-11.
[6]Trend results presented without p-values or raw data--see Table 5-11.

*Data not available; ns = not significant.

tests for the various ETS exposure measures from the studies presented in Table 5-11. The exposure measure most commonly used was intensity of spousal smoking. Eight of the twelve studies that reported exposure-response data based on cigarettes per day showed statistical significance at the $p < 0.05$ level for the trend test. Again, the probability of this many statistically significant results occurring by chance in this number of studies is negligible ($p < 10^{-7}$). The trend test results for the other exposure measures were consistent, in general, with those based on cigarettes per day (three of six studies using total years of exposure were significant, as were two of two studies using pack-years).

Overall, 10 of the 14 studies with sufficient exposure-response data show statistically significant trends for one or more exposure measures. No possible confounder has been hypothesized that could explain the increasing incidence of lung cancer with increasing exposure to ETS in so many independent studies from different countries.

By country, the number of studies with significant results for upward trend is as follows: China, 1 of 2; Greece, 2 of 2; Hong Kong, 1 of 2; Japan, 3 of 3; Sweden, 0 of 1; and United States, 3 of 4. Of particular interest, two of the U.S. studies, GARF and CORR, are statistically significant for a test of trend, providing evidence for an association between ETS exposure and lung cancer even though neither was significant in a test for effect. In both cases, this occurs because the data supporting an increase in RR are largely at the highest exposure level. It appears that relatively high exposure levels are necessary to observe an effect in the United States, as would be expected if spousal smoking is a weaker surrogate for total ETS exposure in this country.

The U.S. study by Fontham et al. (1991), a well-conducted study and the largest case-control study of ETS and lung cancer to date, with the greatest power of all the U.S. studies to detect an effect, was statistically significant with a p-value of 0.04 for the trend test with pack-years as the exposure measure. When the analysis was restricted to adenocarcinomas (the majority of the cases), tests for trend were statistically significant by both years ($p = 0.02$) and pack-years ($p = 0.01$).

5.3.4. Conclusions

Two types of tests have been conducted: (1) a test for effect, wherein subjects must be classified as exposed or unexposed to ETS, generally according to whether the husband is a smoker or not, and (2) a trend test, for which exposed subjects are further categorized by some level of exposure, such as the number of cigarettes smoked per day by the husband, duration of smoking, or total number of packs smoked. Results are summarized in Table 5-13, with countries in the same order as in Table 5-9. Studies are noted in boldface if the test of effect or the trend

Table 5-13. P-values of tests for effect and for trend by individual study[1]

Country	Study	Power	Test	P-value[2]
Greece	KALA	0.39	Effect	0.02
			Trend	0.04
Greece	TRIC	0.45	Effect	<0.01
			Trend	<0.01
Hong Kong	CHAN	0.43	Effect	>0.50
Hong Kong	KOO	0.43	Effect	0.06
			Trend	0.16
Hong Kong	LAMT	0.73	Effect	<0.01
			Trend	<0.01
Hong Kong	LAMW	0.39	Effect	<0.01
Japan	AKIB	0.42	Effect	0.05
			Trend	0.03
Japan	HIRA(Coh)	0.75	Effect	0.04
			Trend	<0.01
Japan	INOU	0.17	Effect	0.07(0.05)[3]
			Trend	0.03
Japan	SHIM	0.37	Effect	0.38
Japan	SOBU	0.66	Effect	0.01
United States	BROW	0.15	Effect	0.28
United States	BUFF	0.17	Effect	>0.50
United States	BUTL(Coh)	0.18	Effect	0.17
United States	CORR	0.22	Effect	0.10(0.005)[3]
			Trend	0.01
United States	FONT	0.93	Effect	0.03[4]
			Trend	0.04[4]
United States	GARF	0.60	Effect	0.12(0.01)[3]
			Trend	<0.02
United States	GARF(Coh)	0.92	Effect	0.18

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Table 5-13. (continued)

Country	Study	Power	Test	P-value[2]
United States	HUMB	0.20	Effect Trend	0.10 ns
United States	JANE	0.44	Effect	>0.50
United States	KABA	0.17	Effect	>0.50
United States	WU	0.21	Effect	0.29
W. Europe				
Scotland	Hole(Coh)	0.09	Effect	0.26
England	LEE	0.20	Effect	0.50
Sweden	PERS	0.45	Effect Trend	0.27(0.02)[3] 0.12
Sweden	SVEN	0.24	Effect	0.31
China	GAO	0.66	Effect Trend	0.18(0.02)[3] 0.29
China	GENG	0.32	Effect Trend	0.01 <0.05
China	LIU	0.18	Effect	>0.50
China	WUWI	0.89	Effect	>0.50

[1]Test for effect--H_0: no increase in lung cancer incidence in never-smokers exposed to spousal ETS; H_A: an increase. Test for trend--H_0: no increase in lung cancer incidence as exposure to spousal ETS increases; H_A: an increase. P-values less than 0.05 are in boldface.
[2]Smallest p-value is used when there is more than one test for trend; ns = not significant.
[3]P-value in parentheses applies to test for effect at highest exposure only (see text).
[4]For all cell types. P-values for adenocarcinoma alone were smaller.

test is significant at 0.05 (one-tailed) or if, as in PERS and GAO, only the odds ratio at the highest exposure is significant. In 8 of the 11 studies in Greece, Hong Kong, or Japan, at least one of the tests is significant at 0.05. For the United States and Western Europe, 4 of the 15 studies are significant at 0.05 for at least one test. For the studies within the first group of countries (Greece, Hong Kong, and Japan), the median power is 0.43, and only 1 of the 10 studies (10%) has power less than 0.25 (INOU). In contrast, the median power for the United States and Western Europe together is 0.21, and 10 of the 15 studies (67%) have power less than 0.25. In a

small study, significance is meaningful, but nonsignificance is not very informative because there is little chance of detecting an effect when there is one. Consequently, there are several studies in the United States-Western Europe group that provide very little information. Two of the four studies in China are significant at the 0.05 level for at least one test. The two nonsignificant studies in China (LIU and WUWI) are not very informative on ETS for reasons previously described (see Section 5.3.2.1).

For the U.S. and Western Europe studies, 3 of the 5 with power greater than 0.25 are shown in boldface (FONT, GARF, and PERS), indicating at least suggestive evidence of an association between ETS and lung cancer, compared with only 1 of 10 with power under 0.25 (CORR). All three of the higher power studies are significant for effect (PERS and GARF are significant at the highest exposure only) and two (FONT and GARF) are also significant for trend. CORR is significant for trend and for effect at the highest exposure level. Overall, the evidence of an association in the United States and Western Europe is strengthened by the tests at the highest exposure levels and by the tests for trend.

To summarize, the results of the several different analyses in this section provide substantial evidence that exposure to ETS from spousal smoking is associated with increased lung cancer mortality. The evidence is strongest in Greece, Hong Kong, Japan, and the United States. The evidence for Western Europe appears similar to that in the United States, but there are far fewer studies. (The usefulness of statistical information from studies in China is quite limited, so no conclusions are drawn from the studies there.)

The evidence from the individual studies, without pooling within each country, is also conclusive of an association. Adjustment, on an individual study basis, for potential bias due to smoker misclassification results in slightly lower relative risk estimates but does not affect the overall conclusions. The results based on either the test for effect or the test for trend cannot be attributed to chance alone. Tests for effect, tests at the highest exposure levels, and tests for trend jointly support the conclusion of an association between ETS and lung cancer in never-smokers.

5.4. STUDY RESULTS ON FACTORS THAT MAY AFFECT LUNG CANCER RISK

5.4.1. Introduction

The possibility of chance accounting for the observed associations between ETS and lung cancer has been virtually ruled out by the statistical methods previously applied. Potential sources of bias and confounding must still be considered to determine whether they can explain the observed increases. While the exposure-response relationships reviewed in Section 5.3.3.3 generally reduce the likelihood of bias and confounding accounting for the observed associations, this section focuses on specific factors that may bias or modify the lung cancer results.

Validity is the most relevant concern for hazard identification. Generalizability of results to the national population (depending on "representativeness" of the sample population, treated in the text) is important for the characterization of population risk, but no more so than validity. As stated by Breslow and Day (1980), "In an analysis, the basic questions to consider are the degree of association between risk for disease and the factors under study, the extent to which the observed associations may result from bias, confounding and/or chance, and the extent to which they may be described as causal."

Whereas Section 5.3 examined the epidemiologic data by individual study and by pooling results by country, this section considers potential sources of bias and confounding and their implications for interpretation of study results. As indicated in the brief review of the meanings of bias and confounding at the end of this section, confounding arises from the characteristics of the sample population, whereas bias is the result of individual study features involving design, data collection, or data analysis. Section 5.4.2 briefly reviews the evidence on non-ETS risk factors and modifiers of lung cancer incidence that appears in the 30 epidemiologic studies (not counting KATA) reviewed for this report. None of the factors has been established as a confounder of ETS, which would require demonstrating that the factor causes lung cancer and is correlated with ETS exposure (specifically, spousal smoking to affect the analysis in this report).

Our objective is to consider the influence of sources of uncertainty on the statistical measures summarized in Table 5-13, although there are limitations to such an endeavor. For example, not controlling for a factor such as age in the statistical analysis, which should be done whether or not the study design is matched on age, may require reanalyzing data not included in the study report. Potential sources of bias are just that--*potential*--and their actual effect may be impossible to evaluate (e.g., selection bias in case-control studies). Although numerous questions of interest cannot be answered unequivocally, or even without a measure of subjective judgment, it is nevertheless worthwhile to consider issues that may affect interpretation of the quantitative results. The issues of concern are largely those of epidemiologic investigations in general that motivate the conscientious investigator to implement sound methodology. Statistical uncertainty aside, the outcomes of studies that fare well under close examination inspire more confidence and thus deserve greater emphasis than those that do poorly.

Preliminary to the next sections, some relevant notes on epidemiologic concepts are excerpted from two IARC volumes entitled *Statistical Methods in Cancer Research* (Breslow and Day, 1980, 1987), dealing with case-control and cohort studies, respectively, which are excellent references. In the interest of brevity, an assortment of relevant passages is simply quoted directly from several locations in the references (page numbers and quotation marks have been omitted to

improve readability). Some readers may wish to skip to the next section; those interested in a more fluid, cogent, and thorough presentation are referred to the references.

- Bias and confounding. The concepts of bias and confounding are most easily understood in the context of cohort studies, and how case-control studies relate to them. Confounding is intimately connected to the concept of causality. In a cohort study, if some exposure E is associated with disease status, then the incidence of the disease varies among the strata defined by different levels of E. If these differences in incidence are caused (partially) by some other factor C, then we say that C has (partially) confounded the association between E and the disease. If C is not causally related to disease, then the differences in incidence cannot be caused by C, thus C does not confound the disease/exposure association.

  Confounding in a case-control study has the same basis as in a cohort study . . . and cannot normally be removed by appropriate study design alone. An essential part of the analysis is an examination of possible confounding effects and how they may be controlled.

  Bias in a case-control study, by contrast, [generally] arises from the differences in design between case-control and cohort studies. In a cohort study, information is obtained on exposures before disease status is determined, and all cases of disease arising in a given time period should be ascertained. Information on exposure from cases and controls is therefore comparable, and unbiased estimates of the incidence rates in the different subpopulations can be constructed. In case-control studies, however, information on exposure is normally obtained after disease status is established, and the cases and controls represent samples from the total. Biased estimates of incidence ratios will result if the selection processes leading to inclusion of cases and controls in the study are different (selection bias) or if exposure information is not obtained in a comparable manner from the two groups, for example, because of differences in response to a questionnaire (recall bias). Bias is thus a consequence of the study design, and the design should be directed towards eliminating it. The effects of bias are often difficult to control in the analysis, although they will sometimes resemble confounding effects and can be treated accordingly.

  To summarize, confounding reflects the causal association between variables in the population under study, and will manifest itself similarly in both cohort and case-control studies. Bias, by contrast, is not a property of the underlying population. It results from inadequacies in the design of case-control studies, either in the selection of cases or controls or from the manner in which the data are acquired.

- On prospective cohort studies. One of the advantages of cohort studies over case-control studies is that information on exposure is obtained before disease status is ascertained. One can therefore have considerable confidence that errors in measurement are the same for individuals who become cases of the disease of interest, and the remainder of the cohort. The complexities possible in retrospective case-control studies because of differences in recall between cases and controls do not apply. [Regarding the success of a cohort study, the] follow-up over time . . . is the essential feature. . . . The success with which the follow-up is achieved is probably the basic measure of the quality of the study. If a substantial proportion of the cohort

is lost to follow-up, the validity of the study's conclusions is seriously called into question.

- On case-control studies. Despite its practicality, the case-control study is not simplistic and it cannot be done well without considerable planning. Indeed, a case-control study is perhaps the most challenging to design and conduct in such a way that bias is avoided. Our limited understanding of this difficult study design and its many subtleties should serve as a warning--these studies must be designed and analyzed carefully with a thorough appreciation of their difficulties. This warning should also be heeded by the many critics of the case-control design. General criticisms of the design itself too often reflect a lack of appreciation of the same complexities which make these studies difficult to perform properly.

  The two major areas where a case-control study presents difficulties are in the selection of a control group, and in dealing with confounding and interaction as part of the analysis. . . these studies are highly susceptible to bias, especially selection bias which creates non-comparability between cases and controls. The problem of selection bias is the most serious potential problem in case-control studies. . . . Other kinds of bias, especially that resulting from non-comparable information from cases and controls are also potentially serious; the most common of these is recall . . . bias which may result because cases tend to consider more carefully than do controls the questions they are asked or because the cases have been considering what might have caused their cancer.

In addition to standard demographic factors (e.g., age) that are usually controlled for in a study, a number of other variables have been considered as potential risk factors (including risk modifiers) for lung cancer. If a factor increases the risk of lung cancer and its presence is correlated with exposure to spousal ETS, then it could be a confounder of ETS if not controlled for in a study's analysis. In general, factors that may affect risk of lung cancer and also may be correlated with ETS exposure are of interest as possible explanatory variables. Findings from the ETS studies are reviewed for six general categories: (1) personal history of lung disease, (2) family history of lung disease, (3) heat sources, (4) cooking with oil, (5) occupation, and (6) diet. Table 5-14 provides an overview of results in these categories. Two shortcomings are common in the studies where these factors appear: failure to evaluate the correlation of exposure to the factor and to ETS, and then to adjust the analysis accordingly; and failure to adjust significance levels for multiple comparisons. Multiple tests on the same data increase the chance of a false positive (i.e., outcomes appear to be more significant than warranted due to the multiple comparisons being made on the same data).

5.4.2. History of Lung Disease

Results regarding history of lung disease have been reported in eight of the reviewed ETS studies, but with little consistency. Tuberculosis (TB), for example, is significantly associated with lung cancer in GAO (OR = 1.7; 95% C.I. = 1.1, 2.4) but not in SHIM (OR = 1.1, no other

Table 5-14. Other risk-related factors for lung cancer evaluated in selected studies

Category	Possible risk factor	Mixed outcome	No evidence
Personal or family history	WU (US) GENG (Ch) LIU (Ch)	SHIM (Jap) GAO (Ch)	
Heat source for cooking or heating	WU (US) WUWI (Ch) GENG (Ch) GAO (Ch) LIU (Ch)	SOBU (Jap)	LAMW (HK)
Cooking with oil	WUWI (Ch) GAO (Ch)		
Diet	WU (US)	KALA (Gr) HIRA (Jap)	SHIM (Jap)
β-carotene			WUWI (Ch) KALA (Gr) GAO (Ch)-harmful
Occupation	WUWI (Ch) SHIM (Jap) GENG (Ch) BUTL (US) BUFF (US)		WU (US) GAO (Ch)

statistics), LIU or WU (no ORs provided). Chronic bronchitis, on the other hand, is nonsignificant in GAO (OR = 1.2; 95% C.I. = 0.8, 1.7), SHIM (OR = 0.8), KABA, and WU, but it is highly significant in LIU (OR = 7.37; 95% C.I. = 2.40, 22.66 for females; OR = 7.32; 95% C.I. = 2.66, 20.18 for males) and mildly so in WUWI (OR = 1.4; 95% C.I. = 1.2, 1.8). (Notably, the populations of WUWI, LIU, and GENG were exposed to non-ETS sources of household smoke.) Consideration of each lung disease separately, as presented, ignores the effect of multiple comparisons described above. For example, GAO looked at five categories of lung disease. If that were taken into account, TB would no longer be significant. No discussion of the multiple comparisons effect was found in any of the references, which might at least be acknowledged.

Broadening our focus to examine the relationship of lung cancer to history of lung disease in general does little to improve consistency. GENG reports an adjusted OR of 2.12 (95% C.I. = 1.23, 3.63) for history of lung disease, GAO's disease-specific findings are consistently positive, and WUWI reports three positive associations out of an unknown number assessed. SHIM and

WU, however, consistently found no effect except marginally for silicosis (perhaps better construed as an occupational exposure surrogate) in SHIM and for childhood pneumonia in WU. LIU found a significant association only for chronic bronchitis and KABA only for pneumonia. Interpretation is hampered by the lack of numerical data for factors that were not statistically significant in KABA, LIU, and WU. Even with such data, however, interpretation is hampered by the absence of control for key potential confounders in many of the studies (e.g., age in GENG and LIU). Only one study (WU) attempted to control for a history variable (childhood pneumonia), which reportedly did not alter the ETS results. The importance of prior lung disease as a factor in studies of ETS is thus unclear, but it does not appear to distort results one way or the other.

5.4.3. Family History of Lung Disease

Only a few of the studies addressed family history of lung disease. GAO found no significant association between family history of lung cancer and subjects' disease status (e.g., parental lung cancer OR = 1.1; 95% C.I. = 0.6, 2.3), and positive family histories were very rare (e.g., 1.0% among mothers of either cases or controls). In contrast, WUWI reports a significant association with history of lung cancer in first-degree relatives (OR = 1.8; 95% C.I. = 1.1, 3.0), which occurred in about 4.5% of the cases. The presence of TB in a household member (OR = 1.6; 95% C.I. = 1.2, 2.1) is also significant, even after adjustment for personal smoking and TB status. The rarity of family-linked lung cancer in these populations makes accurate assessment difficult and also reduces the potential impact on results of any effect it may have. Its study in populations where such cancer is more common would be more appropriate. The household TB outcome may be the result of multiple comparisons and/or confounding, particularly in view of the weaker (nonsignificant) outcome noted for *personal* TB status.

5.4.4. Heat Sources for Cooking or Heating

Household heating and cooking technologies have received considerable attention as potential lung cancer risk factors in Asian ETS studies. Most studies have focused on fuel type. Kerosene was specifically examined in three studies. All three found positive associations--CHAN and LAMW for kerosene cooking, and SHIM for kerosene heating--but none of the associations were statistically significant, and the SHIM relationship held only for adult and not for childhood exposure. Five studies specifically examined coal. GENG evaluated use of coal for cooking and found a significant positive association. Use of coal for household cooking or heating prior to adulthood is significantly associated with lung cancer in WU's study of U.S. residents, but

no results for adulthood are mentioned. Recent charcoal stove use showed a positive (OR = 1.7) but not significant association in SHIM. Separate analyses of five coal-burning devices and two non-coal-burning devices by WUWI found positive although not always significant associations for the coal burners. In contrast, SOBU found no association between use of unventilated heating devices--including mostly kerosene and coal-fueled types but also some wood and gas burners--and lung cancer (OR = 0.94 for use at age 15, 1.09 at age 30, 1.07 at present). Results for wood or straw cooking were specifically reported in three studies. SOBU found a significant association for use of wood or straw at age 30 (OR = 1.89; 95% C.I. = 1.16, 3.06) but only a weak relationship at age 15. GAO found no association with current use of wood for cooking (OR = 1.0; 95% C.I. = 0.6, 1.8), and WUWI mentions that years of household heating with wood, central heating, and coal showed nonsignificant trends (negative, negative, and positive, respectively).

Overall, studies that examined heating and cooking fuels generally found evidence of an association with lung cancer for at least one fuel, which was usually but not always statistically significant. Such relationships appeared most consistently for use of coal and most prominently in WUWI and LIU. Neither study found a significant association between ETS and lung cancer, nor did either address whether coal use was associated with ETS exposure. The presence of non-ETS sources of smoke within households, however, may effectively mask detection of any effect due to ETS (as noted by the authors of WUWI). Evidence of effects of other fuel types and devices is more difficult to evaluate, particularly because many studies do not report results for these factors, but kerosene-fueled devices seem worthy of further investigation.

5.4.5. Cooking With Oil

Cooking with oil was examined by GAO and WUWI, both conducted in China, with positive associations for deep-frying (OR ranges of 1.5-1.9 and 1.2-2.1, respectively, both increasing with frequency of cooking with oil). GAO also reports positive findings for stir-frying, boiling (which in this population often entails addition of oil to the water), and smokiness during cooking and found that most of these effects seemed specific for users of rapeseed oil. These results may apply to other populations where stir-frying and certain other methods of cooking with oil are common. Neither study, however, addressed whether use of cooking with oil is correlated with ETS exposure.

5.4.6. Occupation

Seven studies investigated selected occupational factors, with five reporting positive outcomes for one or more occupational variables. The outcomes, however, are somewhat inconsistent. SHIM found a strong and significant relationship with occupational metal exposure

(OR = 4.8) and a nonsignificant one with coal, stone, cement, asbestos, or ceramic exposure, while WUWI found significant positive relationships for metal smelters (OR = 1.5), occupational coal dust (OR = 1.5), and fuel smoke (OR = 1.6) exposure. Textile work is positively associated with lung cancer in KABA and negatively associated with lung cancer in WUWI. BUFF divided occupations into nine categories plus housewife and found eight positive and one negative associations relative to housewives, but only one ("clerical") is significant. GAO, on the other hand, found no association with any of six occupational categories, while GENG found a significant association for an occupational exposure variable that encompassed textiles, asbestos, benzene, and unnamed other substances (OR = 3.1; 95% C.I. = 1.58, 6.02). WU reported "no association between any occupation or occupational category," although there was a nonsignificant excess among cooks and beauticians. Finally, BUTL(Coh) found an increased RR for wives whose husbands worked in blue collar jobs (> 4; never-smoker). HIRA(Coh) did not present findings for husband's occupation as a risk factor independently but reported that adjustment for this factor did not alter the study's ETS results. Few studies attempted to adjust ETS findings for occupational factors--SHIM found only modest effects of such adjustment for occupational metal exposure, despite an apparent strong independent effect for this factor, and GENG found only minimal effect of occupational exposure on active smoking results but did no adjustment of ETS results. Overall, multiple comparisons, other factors (e.g., socioeconomic status, age), and the rarity of most specific occupational exposure sources probably account for the inconsistent role of occupation in these studies.

5.4.7. Dietary Factors

Investigations related to diet have been reported in nine of the ETS studies, with mixed outcomes. The fundamental difficulty lies in obtaining accurate individual values for key nutrients of interest, such as β-carotene. The relatively modest size of most ETS study populations adds further uncertainty in attempts to detect and assess any dietary effect that, if present, is likely to be small. In those studies where dietary data were collected and adjusted for in the analysis of ETS, diet has had no significant effect. Nevertheless, diet has received attention in the literature as a possible explanatory factor in the observed association between ETS exposure and lung cancer occurrence (e.g., Koo, 1988; Koo et al., 1988; Sidney et al., 1989; Butler, 1990, 1991; Marchand et al., 1991); therefore, a more detailed and specific discussion is provided in this section.

Diet is of interest for a potential protective effect against lung cancer. If nonsmokers unexposed to passive smoke have a lower incidence of spontaneous (unrelated to tobacco smoke) lung cancer incidence due to a protective diet, then the effect would be upward bias in the RR for

ETS. However, for diet to *explain* fully the significant association of ETS exposure in Greece, Hong Kong, Japan, and the United States, which differ by diet as well as other lifestyle characteristics, it would need to be shown that in *each* country: (1) there is a diet protective against lung cancer from ETS exposure, (2) diet is inversely associated with ETS exposure, and (3) the association is strong enough to produce the observed relationship between ETS and lung cancer. Diet may modify the magnitude of any lung cancer risk from ETS (conceivably increase or decrease risk, depending on dietary components), but that would not affect whether ETS is a lung carcinogen.

The literature on the effect of diet on lung cancer is not consistent or conclusive, but taken altogether there may be a protective effect from a diet high in β-carotene, vegetables, and possibly fruits. Also, there is some evidence that low consumption of these substances may correlate with increased ETS exposure, although not necessarily for all study areas. The calculations made by Marchand et al. (1991) and Butler (1990, 1991) are largely conjectural, being based only on *assumed* data. Therefore, we examined the passive smoking studies themselves for empirical evidence on the effect of diet and whether it may affect ETS results.

It was found that nine of the studies have data on diet, although only five of them use a form of analysis that assesses the impact of diet on the ETS association. None of those five studies--CORR, HIRA(Coh), KALA, SHIM, and SVEN--found that diet made a significant difference. In the four studies where data on diet were collected but not controlled for in the analysis of ETS, three (GAO, KOO, and WUWI) are from East Asia and one (WU) is from the United States. Koo (1988), who found strong protective effects for a number of foods, has been one of the main proponents of the idea that diet may explain the passive smoking lung cancer effect. To our knowledge, however, she has not published a calculation examining that conjecture in her own study where data were collected on ETS subjects. In WU, a protective effect of β-carotene was found, but the data include a high percentage of smokers (80% of the cases for adenocarcinoma, 86% for squamous cell), and the number of never-smokers is small. In recent correspondence concerning the large FONT study, its authors state that "mean daily intake of beta-carotene does not significantly differ between study subjects whose spouse smoked and those whose spouse never smoked" (Fontham et al., 1992).

The equivocal state of the literature regarding the effect of diet on lung cancer is also apparent in the nine ETS studies that include dietary factors, summarized in Table 5-15. Note that GAO found an adverse effect from β-carotene. HIRA and KOO found opposite effects from fish while SHIM found no effect. Fruit was found to be protective by KALA and KOO but adverse by SHIM and WUWI. Retinol (based on consumption of eggs and dairy products) was found to be protective by KOO but adverse by GAO and WUWI.

Table 5-15. Dietary effects in passive smoking studies of lung cancer in females

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
CORR[2]	2.07	Carotene Vitamin A	No data given No data given				Never-smokers. Carotene and total vitamin A were examined. "Except for gender, age, and study area, no confounding was detected."
GAO	1.19	Carotene rich Retinol rich Vitamin A index	1.0 1.0 1.0	1.0 1.1 1.6[3]	1.3 1.0 1.2	2.0[3] 1.1 2.0[3]	Patterns were similar for smokers and nonsmokers. Passive RR was not adjusted for diet, possibly because the trends were the opposite of those in the literature.
HIRA[4]	1.53	Green-yellow veg. Fish Meat Milk Soy paste soup	- - - - -	1.0[5] 1.0 1.0 1.0 1.0	- - - - -	0.86[6] 1.87[3] 0.62 1.30 0.93	Never-smokers. Lung cancer risks for wives whose husbands were former smokers plus 1-19 cig./day smokers and 20+ cig./day smokers relative to never-smokers were 1.50 and 1.79 when adjusted for wives' age (Hirayama, 1984). They ranged from 1.53 to 1.69 and 1.66 to 1.91 when adjusted for wives' age, husband's occupation, and each of the various dietary factors.
KALA	1.92	β-carotene Vegetables Fruits Vitamin C Retinol (preformed)	1.0 1.0 1.0 1.0 1.0	- - - - -	- - - - -	1.01 1.09 0.33[3] 0.67 1.31	Never-smokers. Controlled for age, years of schooling, interviewer, and total energy intake. No confounding was observed between the passive smoking effect and the effect of fruits, or between that of fruits and that of vegetables. Passive risk increased to 2.11 when adjusted for fruit consumption.

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Table 5-15. (continued)

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
KOO[7]	1.55	Leafy green veg.	-	1.0	0.49	0.49	Never-smokers. Values are adjusted for age, numbers of live births, and schooling. Diet items are selected to compare with those in other studies. No calculation is shown of confounding effect of diet on the passive smoking risk either in Koo et al. (1987), Koo (1988), Koo et al. (1988), or Koo (1989). Fresh fruit, vitamin C, fresh fish, and retinol showed statistically significant trends.
		Carrots	-	1.0	1.31	0.51	
		β-carotene	-	1.0	0.73	0.73	
		Fresh fruit	-	1.0	0.81	0.42	
		Vitamin C	-	1.0	0.55	0.47	
		Fresh fish	-	1.0	0.46	0.35	
		Smoked/cured meat/poultry	-	1.0	0.82	0.92	
		Milk	-	1.0	1.66	0.92	
		Retinol	-	1.0	0.55	0.42	
SHIM	1.08	Green-yellow veg.	-	1.0[8]	-	0.9[8]	Never-smokers. No dose response was found. No difference between cases and controls was found regarding intake of green-yellow vegetables.
		Fruit	-	1.0	-	1.2	
		Milk	-	1.0	-	1.0	
		Fish, pork, or lamb	-	1.0	-	1.0	
		Chicken	-	1.0	-	0.7	
SVEN	1.26	Carrots	1.0[9]	0.7[10]	-	0.6[3,11]	Adjusted for age, smoking, cumulative Rn exposure and municipality. The inclusion of carrot consumption in the regression model "had only a slight effect on the risk estimates of the other exposure variables." See Svensson (1988).

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Table 5-15. (continued)

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
WU	1.41	β-carotene	1.0	0.52	0.32	0.40[3]	For adenocarcinoma. Risks of 0.67, 1.0, and 0.63, high calf versus low calf, were observed for β-carotene, preformed vitamin A, and dairy and eggs for squamous cell carcinoma. Adjusted for cigarettes smoked per day. No adjustment is shown to the passive risk for diet.
		Preformed Vit. A	1.0	0.92	0.50	0.83	
		Dairy products and eggs	1.0	0.82	0.63[3]	0.37[3]	
WUWI	0.79	Vegetables					Adjusted for age, education, personal smoking, and study area. Eight variables other than smoking were thought to have a significant effect on lung cancer risk. Diet variables were not included in this list, and no adjustment to the passive risk was made for them.
		high-carotene	1.0	1.1	1.0	0.9	
		low-carotene	1.0	1.0	1.0	0.8	
		Fresh fruit	1.0	1.0	1.4[3]	1.5[3]	
		Animal protein	1.0	1.6[3]	1.6[3]	2.3[3]	

[1]From Table 5-5.
[2]As reanalyzed by Dalager et al. (1986).
[3]Statistically significant at the p = 0.05 level.
[4]Case-control study nested in Hirayama's cohort study, ages 40-69 only (Hirayama, 1989).
[5]Less than daily.
[6]Daily.
[7]From Koo (1988).
[8]Cutoffs various.
[9]Less than once per week.
[10]Once per week.
[11]More than once per week.

In view of the results summarized in Tables 5-14 and 5-15, the actual data of ETS studies do not support the suspicion that diet introduces a systematic bias in the ETS results. Indeed, it would be difficult to show otherwise. Dietary intake is difficult to assess; dietary habits vary within countries and enormously between countries, making it difficult to attribute any effect on lung cancer to a particular food group; lifestyle characteristics and consumption of food and beverage with possibly an adverse effect may be associated, either positively or negatively, with the food group under consideration. It would, of course, be helpful to identify dietary factors that may affect lung cancer, positively or negatively, because that information could usefully contribute to public health. To affect interpretation of ETS results, however, it would need to be established also that consumption of the dietary factor of interest is highly correlated with ETS exposure in study populations where ETS exposure is linked with increased incidence of lung cancer.

5.4.8. Summary on Potential Modifying Factors

In summary, an examination of six non-ETS factors that may affect lung cancer risk finds none that explains the association between lung cancer and ETS exposure as observed by independent investigators across several countries that vary in social and cultural behavior, diet, and other characteristics. On the other hand, the high levels of indoor air pollution from other sources (e.g., smoky coal) that occur in some parts of China and show statistical associations with lung cancer in the studies of GENG, LIU, and WUWI may mask any ETS effects in those studies.

5.5. ANALYSIS BY TIER AND COUNTRY

In this section, attention is directed to properties of individual studies, including potential sources of bias, that may affect their utility for the assessment of ETS and lung cancer. Studies are assessed based on qualitative as well as statistical evaluation. The studies are qualitatively reviewed in Appendix A and categorized into "tiers" within country. Studies are individually scored according to items in eight categories. Study scores are then implemented in a numerical scheme to classify each study into one of four tiers according to that study's assessed utility for hazard identification of ETS. Tier 1 studies are those of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. Tier 4 is reserved for studies we would exclude from analysis for ETS, for various reasons specified in the text. In the statistical analysis presented in this section, the summary RR for each country is recalculated for studies in Tier 1 alone and for Tiers 1-2, 1-3, and 1-4 (the last category corresponds to the combined analysis shown in

Table 5-9) by country. This exercise provides some idea of the extent to which the summary RR for a country depends on the choice of studies.

The assignment of studies to tiers is shown in Table 5-16. Overall, 5 studies are in the highest tier, while 15, 5, and 5 studies are in Tiers 2, 3, and 4, respectively (KATA was not assigned to a tier). Studies in Tier 4 are not recommended for the objectives of this report. The statistical weight for Tiers 1, 2, and 3 pooled together for each country is shown in Table 5-9 as a percentage of the total for corresponding tiers over all countries. Emphasis on studies through Tier 2 or through Tier 3 is somewhat arbitrary. Although studies in Tier 1 are judged to be of the highest utility, exclusive attention to Tier 1 would eliminate considerable epidemiologic data because only 16% of the studies are in Tier 1. Excluding Tier 4 leaves the choices to either all studies through Tier 2 or through Tier 3. GAO is the only study in China that was not placed in Tier 4, but there is little basis to assume that this single study from Shanghai should be representative of a vast country like China.

Table 5-17 presents adjusted relative risk estimates, 90% confidence intervals, and significance levels (one-sided) from studies pooled by country and by tier. The pooled relative risks do not decrease as the results from studies in Tier 2 and Tier 3 are combined with those from Tier 1, with two exceptions: In the United States, the pooled estimate changes from 1.28 to 1.22 to 1.19 when Tier 2 and Tier 3 studies are added, respectively, and in Western Europe, the pooled estimate changes from 1.21 to 1.17 when Tier 2 studies are added. The pooled estimates for studies through Tier 2 are statistically significant at $p = 0.02$ (one-tailed) in Greece, Hong Kong, Japan, and the United States; Western Europe is the exception ($p = 0.22$). The same statement holds with Tier 2 replaced by Tier 3, except that China includes one study at $p = 0.18$. The relative risk results from all four Western European studies (RR = 1.17) is virtually the same for all U.S. studies (RR = 1.19), but with less power that value is not significant for Western Europe. The similarity of outcomes is also interesting, however, because Western Europe is probably more similar to the United States than the other countries.

Analysis by tiers provides a methodology for weighting studies according to their utility for hazard identification of ETS. It allows one to emphasize those studies thought to provide better data for analysis of an ETS effect. The addition of studies of lower utility to the analysis, such as inclusion of Tier 3 studies with those from Tiers 1 and 2, has a small effect on the relative risk estimate but both increases its statistical significance and narrows its confidence interval. In view of that outcome and the results and discussion in Section 5.4, this analysis finds little to indicate confounding or bias in studies through Tier 3 (which include all studies in the United States). In summary, it is concluded that the association of ETS and lung cancer observed from

Table 5-16. Classification of studies by tier

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
Greece	KALA	X			
Greece	TRIC			X	
Hong Kong	KOO	X			
Hong Kong	LAMT		X		
Hong Kong	LAMW			X	
Hong Kong	CHAN				X
Japan	AKIB		X		
Japan	HIRA(Coh)		X		
Japan	SHIM		X		
Japan	SOBU		X		
Japan	INOU				X
United States	FONT	X			
United States	BUTL(Coh)		X		
United States	GARF		X		
United States	HUMB		X		
United States	JANE		X		
United States	WU		X		
United States	BROW		X		
United States	BUFF			X	
United States	CORR		X		
United States	GARF(Coh)			X	
United States	KABA		X		

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Table 5-16. (continued)

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
W. Europe					
Scotland	HOLE(Coh)	X			
Sweden	PERS	X			
Sweden	SVEN		X		
England	LEE		X		
China	GAO			X	
China	GENG				X
China	LIU				X
China	WUWI				X

the analysis of 30 epidemiologic studies in eight different countries is not due to chance alone and is not attributable to bias or confounding.

5.6. CONCLUSIONS FOR HAZARD IDENTIFICATION

5.6.1. Criteria for Causality

According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria [that] must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

As demonstrated in the preceding sections, the overall results observed in the 30 epidemiologic studies are not attributable to chance and the association between ETS and lung cancer is not explained by bias or confounding.

Table 5-17. Summary data interpretation by tiers within country[1]

Through Tier[2]	Relative weight[3] (%)	Country[4]	Studies added	RR	Confidence interval 90%	P-value effect
1		Greece	KALA	1.92	(1.13, 3.23)	0.02
2	4	**Greece**	---	**1.92**	**(1.13, 3.23)**	**0.02**
3	6	**Greece**	TRIC	**2.01**	**(1.42, 2.84)**	**0.0005**
4		Greece	---	2.01	(1.42, 2.84)	0.0005
1		Hong Kong	KOO	1.54	(0.98, 2.43)	0.06
2	16	**Hong Kong**	LAMT	**1.61**	**(1.25, 2.07)**	**0.0009**
3	14	**Hong Kong**	LAMW	**1.75**	**(1.39, 2.19)**	**0.00002**
4		Hong Kong	CHAN	1.48	(1.21, 1.81)	0.0008
1		Japan	---	---	---	---
2	30	**Japan**	AKIB, HIRA(Coh), SHIM, SOBU	**1.39**	**(1.16, 1.66)**	**0.001**
3	23	**Japan**	---	**1.39**	**(1.16, 1.66)**	**0.001**
4		Japan	INOU	1.41	(1.18, 1.69)	0.0007
1		United States	FONT	1.28	(1.03, 1.60)	0.03
2	41	**United States**	BUTL(Coh), CORR, GARF, HUMB, JANE, KABA, WU	**1.22**	**(1.04, 1.42)**	**0.02**
3	43	**United States**	BROW, BUFF, GARF(Coh)	**1.19**	**(1.04, 1.35)**	**0.02**
4		United States	---	1.19	(1.04, 1.35)	0.02
1		W. Europe	HOLE(Coh), PERS	1.21	(0.79, 1.90)	0.24
2	9	**W. Europe**	SVEN, LEE	**1.17**	**(0.85, 1.64)**	**0.22**
3	7	**W. Europe**	---	**1.17**	**(0.85, 1.64)**	**0.22**
4		W. Europe	---	1.17	(0.85, 1.64)	0.22
1		China	---	---	---	---
2	0	**China**	---	---	---	---
3	7	**China**	GAO	**1.19**	**(0.87, 1.62)**	**0.18**
4		China	GENG, LIU, WUWI	0.95	(0.81, 1.12)	0.70

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Table 5-17. (continued)

[1]Use of Tiers 1 through 2 or Tiers 1 through 3, both shown in boldface, is recommended. Tier 4 is *not* recommended.
[2]Each line contains the studies in the previous tiers plus those added.
[3]Percentage of total weight by country for Tiers 1 through 2 or 1 through 3.
[4]Western Europe consists of England, Scotland, and Sweden.

Below, the evidence for a causal association between ETS and lung cancer is evaluated according to seven specific criteria for causality developed by an EPA workshop to supplement the *Guidelines* (U.S. EPA, 1989). These criteria are similar to the original and classical recommendations of Hill (1953, 1965). The seven recommended (but not official) criteria from the EPA workshop, which vary between essential and desirable, are listed below (U.S. EPA, 1989).

> A causal interpretation is enhanced for studies to the extent that they meet the criteria described below. None of these actually establishes causality; actual proof is rarely attainable when dealing with environmental carcinogens. The absence of any one or even several of the others does not prevent a causal interpretation. Only the first criterion (temporal relationship) is essential to a causal relationship: with that exception, none of the criteria should be considered as either necessary or sufficient in itself. The first six criteria apply to an individual study. The last criterion (coherence) applies to a consideration of all evidence in the entire body of knowledge.

1. Temporal relationship: The disease occurs within a biologically reasonable timeframe after the initial exposure to account for the specific health effect.

2. Consistency: When compared to several independent studies of a similar exposure in different populations, the study in question demonstrates a similar association which persists despite differing circumstances. This usually constitutes strong evidence for a causal interpretation (assuming the same bias or confounding is not also duplicated across studies).

3. Strength of association: The greater the estimate of risk and the more precise, the more credible the causal association.

4. Dose-response or biologic gradient: An increase in the measure of effect is correlated positively with an increase in the exposure or estimated dose. If present, this characteristic should be weighted heavily in considering causality. However, the absence of a dose-response relationship should not be construed by itself as evidence of a lack of a causal relationship.

5. Specificity of the association: In the study in question, if a single exposure is associated with an excess risk of one or more cancers also found in other studies, it increases the likelihood of a causal interpretation.

6. Biological plausibility: The association makes sense in terms of biological knowledge. Information from toxicology, pharmacokinetics, genotoxicity, and in vitro studies should be considered.

7. Coherence: Coherence exists when a cause-and-effect interpretation is in logical agreement with what is known about the natural history and biology of the disease. A proposed association that conflicted with existing knowledge would have to be examined with particular care. (This criterion has been called "collateral evidence" previously.)

5.6.2. Assessment of Causality

We consider the extent to which the criteria for causality are satisfied for the ETS studies. Regarding *temporal relationship*, ETS exposure classification is typically based on the marital history of a subject, which varies, or on the status at the beginning of a prospective cohort study. Very few studies up through Tier 3 considered current exposure status only (see Appendix A), so some history of ETS exposure is largely the rule for ETS-exposed subjects. Analysis of data by exposure level in Section 5.3.3 indicates increased relative risk with exposure level, which supports the temporal relationship.

If ETS causes lung cancer, then the true relative risk is small for detection by epidemiologic standards and may differ between countries as well. However, by considering the totality of the evidence, it is determined that the large accumulation of epidemiologic evidence from independent sources in different locales and circumstances, under actual exposure conditions, is adequate for conclusiveness. Having accounted for variable study size, adjusted for a possible systematic spousal bias due to smoker misclassification, and considered potential bias, confounding, and other sources of uncertainty on a study-by-study basis, *consistency* of a significant association is clearly evident for the summary statistical measures for Tiers 1 through 2 and 1 through 3 in Greece, Hong Kong, Japan, and the United States. The combined countries from Western Europe are similar in outcome to the United States, although significance is not attained. There is too much obscurity and uncertainty attached to the studies in China for adequate data interpretation.

The relative risks for each country are obtained by pooling estimates from the epidemiologic studies conducted in the country. The *strength of association* is limited by the true value of the relative risk, which is small. Statistical significance is attained, however, for the pooled studies of the United States and most other countries. The data were obtained from actual conditions of environmental exposure; therefore, imprecision is not increased by extrapolation of results from atypically high exposure concentrations, a common situation in risk analysis. Additionally, all studies were individually corrected for systematic bias from smoker misclassification at the outset, and qualitative characteristics of the studies were carefully reviewed to emphasize the results from the studies with higher utility for the objectives of this report. The outcome for the United States is heavily influenced by the large National Cancer Institute study (FONT) that was specifically designed and executed to avoid methodological problems that might undermine the accuracy or precision of the results.

Of the 14 studies reporting a test for upward trend, 10 are statistically significant at 0.05 (see Table 5-12) which would occur by chance alone with probability less than 10^{-9}. This

evidence of *dose response* is very supportive of a causal interpretation because it would be an unlikely result of any operative sources of bias or confounding.

Specificity does not apply to ETS. Although ETS has been assessed for the same endpoint (lung cancer) in all studies, the occurrence of lung cancer is not specific to ETS exposure. Data on histological cell type are not conclusive. The study by Fontham and colleagues (1991) suggests that adenocarcinoma may be more strongly related to ETS exposure than other cell types. Adenocarcinoma, however, does not appear to be etiologically specific to ETS.

Biomarkers such as cotinine/creatinine levels clearly indicate that ETS is taken up by the lungs of nonsmokers (see Chapter 3). The similarity of carcinogens identified in sidestream and mainstream smoke, along with the established causal relationship between lung cancer and smoking in humans with high relative risks and dose-response relationships in four different lung cell types down to low exposure levels, provide *biological plausibility* that ETS is also a lung carcinogen (Chapter 4). In addition, animal models and genotoxicity assays provide corroborating evidence for the carcinogenic potential of ETS (Chapter 4). The epidemiologic data provide independent empirical verification of the anticipated risk of lung cancer from passive smoking and also an estimate of the increased risk of lung cancer to never-smoking women. The *coherence* of results from these three approaches and the lack of significant arguments to the contrary strongly support causality as an explanation of the observed association between ETS exposure and lung cancer.

5.6.3. Conclusion

Based on the assessment of all the evidence considered in Chapters 3, 4, and 5 of this report and in accordance with the EPA *Guidelines* and the causality criteria above for interpretation of human data, this report concludes that ETS is a Group A human carcinogen, the EPA classification "used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer" (U.S. EPA, 1986a).

6. POPULATION RISK OF LUNG CANCER FROM PASSIVE SMOKING

6.1. INTRODUCTION

The preceding chapter addressed the topic of hazard identification and concluded that environmental tobacco smoke (ETS) exposure is causally associated with lung cancer. If an effect is large enough to detect in epidemiologic studies investigating the consequences of ETS exposure at common exposure levels, the individual risk associated with exposure is considered to be high compared with most environmental contaminants assessed. Of course, the number of lung cancer deaths attributable to ETS exposure for a whole population, such as the United States, depends on the number of persons exposed as well as the individual risk. Studies of cotinine/creatinine concentrations in nonsmokers indicate that ETS is virtually ubiquitous. For example, in urinary bioassays of 663 nonsmokers, Cummings et al. (1990) found that over 90% had detectable levels of cotinine. Among the 161 subjects who reported no recent exposure to ETS, the prevalence of detectable cotinine was still about 80%. Although the average cotinine level for all those tested may be below the average for subjects exposed to spousal ETS, as studied in this report, it indicates uptake of ETS to some extent by a large majority of nonsmokers (see also Chapter 3). Consequently, exposure to ETS is a public health issue that needs to be considered from a national perspective.

This chapter derives U.S. lung cancer mortality estimates for female and male never-smokers and long-term (5+ years) former smokers. Section 6.2 discusses prior approaches to estimating U.S. population risk. Section 6.3 presents this report's estimates. First, the parameters and formulae used are defined (Section 6.3.2), and then lung cancer mortality estimates are calculated from two different data sets and confidence and sources of uncertainty in the estimates are discussed. Section 6.3.3 derives estimates based on the combined relative risk estimates of the 11 U.S. studies from Chapter 5. Section 6.3.4 bases its estimates on the data from the single largest U.S. study, that of Fontham et al. (1991). Finally, Section 6.3.5 discusses the sensitivity of the estimates to changes in various parameter values. ETS-attributable lung cancer mortality rates (LCMR) for each of the individual studies from Chapter 5 are presented in Appendix C.

6.2. PRIOR APPROACHES TO ESTIMATION OF POPULATION RISK

Several authors have estimated the population risk of lung cancer from exposure to ETS. Two approaches have been used almost exclusively. One approach analyzes the overall epidemiologic evidence available from case-control and cohort studies, as done in this report; the other estimates a dose-response relationship for ETS exposure extrapolated from active smoking, based on "cigarette-equivalents" determined from a surrogate measure of exposure common to

passive and active smoking. A recent review of risk assessment methodologies in passive smoking may be found in Repace and Lowrey (1990).

6.2.1. Examples Using Epidemiologic Data

The National Research Council report (NRC, 1986) is a good example of the epidemiologic approach. An overall estimate of relative risk (RR) of lung cancer for never-smokers exposed to both spousal smoking and background ETS versus those exposed only to background ETS is obtained by statistical summary across all available studies. Two "corrections" are then made to the estimate of RR to correct for the two sources of systematic bias. The first correction accounts for expected upward bias from former smokers and current smokers who may be misclassified as never-smokers; this correction results in a decrease in the RR estimate. The second correction is an upward adjustment to the RR taking into account the risk from background exposure to ETS (experienced by a never-smoker whether married to a smoker or not) to obtain estimates of the excess lung cancer risk from all sources of ETS exposure (spousal smoking and background ETS) relative to the risk in an ETS-free environment. Population risk can then be characterized by estimating the annual number of lung cancer deaths among never-smokers attributable to all sources of ETS exposure. This calculation requires the final corrected estimates of RR (one for background ETS only and one for background plus spousal smoking), the annual number of lung cancer deaths (LCDs) from all causes in the population assessed (e.g., never-smokers of age 35 and over), and the proportion of that population exposed to spousal smoking. The entire population is assumed to be exposed to some average background level of ETS; although, in fact, the population contains some individuals with high exposure and others with virtually no exposure.

The NRC report combines data for female and male never-smokers to obtain an overall observed RR estimate of 1.34 (95% confidence interval [C.I.] = 1.18, 1.53), but this estimate is most heavily influenced by the abundant female data. (The female data alone generate a combined RR estimate of 1.32 [95% C.I. = 1.18, 1.52], while the male data produce an RR estimate of 1.62 [95% C.I. = 0.99, 2.64].) To adjust for potential misclassification bias, the NRC uses the construct of Wald and coworkers. The technical details of the adjustment are contained in Wald et al. (1986) and to a lesser degree in the NRC report. After correcting the overall observed RR estimate of 1.34 downward for an expected positive (upward) bias from smoker misclassification, the NRC concludes that the relative risk is about 1.25, and probably lies between 1.15 and 1.35. Correction for background sources (i.e., nonspousal sources of ETS) increases the NRC estimate of RR for an "exposed" person (i.e., exposed to ETS from spousal smoking) to 1.42 (range of 1.24 to 1.61); the change is due only to implicit redefinition of RR to mean risk relative to zero-ETS exposure instead of relative to nonspousal sources of ETS. Under this redefinition, the RR for an

"unexposed" person (i.e., unexposed to spousal ETS) versus a truly unexposed person (i.e., in a zero-ETS environment) becomes 1.14 (range of 1.08 to 1.21). The NRC report further estimates that about 21% of the lung cancers in nonsmoking women and 20% in nonsmoking men may be attributable to exposure to ETS (NRC, 1986, Appendix C); these estimates, however, are based on RRs corrected for background ETS but not for smoker misclassification. Applying these percentages to estimates of 6,500 LCDs in never-smoking women and 3,000 LCDs in never-smoking men in 1988 (American Cancer Society, personal communication), the number attributable to ETS exposure is 1,365 and 600, respectively, for a total of about 2,000 LCDs among never-smokers of both sexes.

Robins (NRC, 1986, Appendix D [included in the NRC report but neither endorsed nor rejected by the committee]) explores three approaches to assessment of lung cancer risk from exposure to ETS, each with attendant assumptions clearly stated. A related article by Robins et al. (1989) contains most of the same information. Method 1 is based solely on evaluation of the epidemiologic data applying two assumptions: (1) correction of relative risk for background exposure to ETS independent of age, and (2) the excess relative risk in a nonsmoker is proportional to the lifetime dose of ETS. In this method, Robins uses a weighted average RR of 1.3. After correcting this RR for background ETS exposure, age-adjusted population-attributable risks are calculated for females and males separately. Adjusting Robins' results to 6,500 annual LCDs in female never-smokers and 3,000 LCDs in male never-smokers, for comparison purposes, yields estimates of 1,870 female LCDs and 470 male LCDs attributable to ETS. Method 2 uses an overall relative risk value based on epidemiologic data, but also makes some assumptions to appeal to results of Day and Brown (1980) and Brown and Chu (1987) on lung cancer risk in active smokers. Again, adjusting Robins' estimates to 6,500 female LCDs and 3,000 male LCDs, the range of excess LCDs attributable to ETS is 1,650 to 2,990 for never-smoking females and 420 to 1,120 for never-smoking males. Method 3 is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

The Centers for Disease Control (CDC) has published an estimate of 3,825 (2,495 female and 1,330 male) deaths in nonsmokers from lung cancer attributable to passive smoking for the year 1988 (CDC, 1991a), with reference to the NRC report of 1986. Those figures are the midrange of values for males and females from method 2 of Robins in Appendix D of the NRC report (NRC, 1986).

Blot and Fraumeni (1986) published a review and discussion of the available epidemiologic studies about the same time that the reports of the Surgeon General and NRC appeared. The set of studies considered by Blot and Fraumeni are almost identical to those included in the NRC report, except for omission of one cohort study (Gillis et al., 1984), and inclusion of Wu et al.

(1985), the case-control study excluded by the NRC because the raw data were unpublished. An overall relative risk estimate calculated from the raw data for females yields 1.3 (95% C.I. = 1.1, 1.5). When the results are combined for high-exposure categories, the overall relative risk estimate is 1.7 (1.4, 2.1).

Wells (1988) provides a quantitative risk assessment that includes several epidemiologic studies subsequent to the NRC and Surgeon General's reports of 1986 (NRC, 1986; U.S. DHHS, 1986). Like the NRC report, the epidemiologic data for both women and men are considered, for which Wells provides separate estimates of overall relative risk and attributable risk. Wells calculates an overall relative risk of 1.44 (95% C.I. = 1.26, 1.66) for females and 2.1 (1.3, 3.2) for males. Following the general approach of Wald et al. (1986), the misclassification percentage for ever-smokers is assumed to be 5% (compared to 7% for Wald et al.). Rates are corrected for background exposure to ETS, except in studies from Greece, Japan, and Hong Kong, where the older nonsmoking women are assumed to experience very little exposure to ETS outside the home. A refinement in the estimation of population-attributable risk is provided by adjusting for age at death (which also appears in the calculations of Robins, NRC, Appendix D). The calculation of population-attributable risk applies to former smokers as well as never-smokers, which is a departure from Wald et al. and the NRC report. The annual number of LCDs attributable to ETS in the United States is estimated to be 1,232 (females) and 2,499 (males) for a total of 3,731. About 3,000, however, is thought to be the best current estimate (Wells, 1988). (In addition to the estimates of ETS-attributable LCDs, Wells uses the epidemiological approach to derive estimates of ETS-attributable deaths from other cancers--11,000--and from heart disease--32,000.)

Saracci and Riboli (1989), of the International Agency for Research on Cancer (IARC), review the evidence from the 3 cohort studies and 11 of the case-control studies (Table 4-1). The authors follow the example of the NRC and Wald et al. with respect to the exclusion of studies, and add only one additional case-control study (Humble et al., 1987). The overall observed relative risk for the studies, 1.35 (95% C.I. = 1.20, 1.53), is about the same as that reported by the NRC, 1.34 (1.18, 1.53). It is not reported how the overall relative risk was calculated.

Repace and Lowrey (1985) suggest two methods to quantify lung cancer risk associated with ETS. One method is based on epidemiologic data, but, unlike the previous examples, Repace and Lowrey use a study comparing Seventh-Day Adventists (SDAs) (Phillips et al., 1980a,b) with a demographically and educationally matched group of non-SDAs who are also never-smokers to obtain estimates of the relative risk of lung cancer mortality, in what they describe as a "phenomenological" approach. The SDA/non-SDA comparison provides a basis for assessing lung cancer risk from ETS in a broader environment, particularly outside the home, than the other epidemiologic studies. It also serves as an independent source of data and an alternative approach

for comparison. Information regarding the number of age-specific LCDs and person-years at risk for the two cohorts is obtained from the study. The basis for comparison of the two groups is the premise that the non-SDA cohort is more likely to be exposed to ETS than the SDA group due to differences in lifestyle. Relatively few SDAs smoke, so an SDA never-smoker is probably less likely to be exposed at home by a smoking spouse, in the workplace, or elsewhere, if associations are predominantly with other SDAs. One of the virtues of this novel approach is that it contributes to the variety of evidence for evaluation and provides a new perspective on the topic.

Phillips et al. (1980 a,b) reported that the non-SDA cohort experienced an average LCMR equal to 2.4 times that of the SDA cohort. Using 1974 U.S. Life Tables, Repace and Lowrey calculate the difference in LCMR for the two cohorts by 5-year age intervals and then apply this value to an estimated 62 million never-smokers in the United States in 1979 to obtain the number of LCDs attributable to ETS annually. The result, 4,665, corresponds to a risk rate of about 7.4 LCDs per 100,000 person-years. In an average lifespan of 75 years, that value equates to 5.5 deaths per 1,000 people exposed. The second method described by Repace and Lowrey is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

Wigle et al. (1987) apply the epidemiologic evidence from the SDA/non-SDA study (Phillips et al., 1980a,b) to obtain estimates of the number of LCDs in never-smokers due to ETS in the population of Canada. The estimated number of deaths from lung cancer attributable to passive smoking is calculated separately for males and females, using age-specific population figures for Canada and the age-specific rates of death from lung cancer attributable to ETS estimated by Repace and Lowrey (1985). A total of 50 to 60 LCDs per year is attributed to spousal smoking alone, with 90% of them in women. Overall, involuntary exposure to tobacco smoke at home, work, and elsewhere may cause about 330 LCDs annually.

6.2.2. Examples Based on Cigarette-Equivalents

The cigarette-equivalents approach assumes that the dose-response curve for lung cancer risk from active smoking also applies to passive smoking, after extrapolation of the curve to lower doses and conversion of ETS exposure into an "equivalent" exposure from active smoking, determined from a surrogate measure of exposure common to passive and active smoking. Relative cotinine concentrations in body fluids (urine, blood, or saliva) of smokers versus nonsmokers and tobacco smoke particulates in sidestream smoke (SS) and mainstream smoke (MS) have commonly been used for this purpose. The lung cancer risk of ETS is assumed to equal the risk from active smoking at the rate determined by the cigarette-equivalents. For example, suppose the average cotinine concentration in exposed never-smokers is 1% of the average value found in people who smoke 30 cigarettes per day. The lung cancer risk for a smoker of (0.01)30 =

0.3 cigarettes per day is estimated by low-dose extrapolation from a dose-response curve for active smoking, and that value is used to describe the lung cancer risk for ETS exposure. This general explanation describes the nature of the approach; however, authors vary in their constructed solutions and level of detail. The basic assumption of cigarette-equivalents procedures is that the lung cancer risks in passive and active smokers are equivalently indexed by the common measure of exposure to tobacco smoke, i.e., a common value of the surrogate measure of exposure in an active and a passive smoker would imply the same lung cancer risk in both. This assumption may not be tenable, however, as MS and SS differ in the relative composition of carcinogens and other components identified in tobacco smoke and in their physicochemical properties in general; the lung and systemic distribution of chemical agents common to MS and SS are affected by their relative distribution between the vapor and particle phases, which differs between MS and SS and changes with SS as it ages. Active and passive smoking also differ in characteristics of intake; for example, intermittent (possibly deep) puffing in contrast to normal (shallow) inhalation, which may affect deposition and systemic distribution of various tobacco smoke components as well (see Sections 3.2 and 3.3.2).

Several authors have taken issue with the validity of the cigarette-equivalents approach. For example, Hoffmann et al. (1989), in discussing the longer clearance times of cotinine from passive smokers than from active smokers, conclude that "the differences in the elimination time of cotinine from urine preclude a direct extrapolation of cigarette-equivalents to smoke uptake by involuntary smokers." A recent consensus report of an IARC panel of experts (Saracci, 1989) states, "Lacking knowledge of which substances are responsible for the well-established carcinogenic effect of MS, it is impossible to accurately gauge the degree of its similarity to ETS in respect to carcinogenic potential." The Surgeon General's report devotes a three-page section to the concept of cigarette-equivalents, quantitatively demonstrating how they can vary as a measure of exposure (U.S. DHHS, 1986). It concludes that "these limitations make extrapolation from atmospheric measures to cigarette-equivalents units of disease risk a complex and potentially meaningless process." (On a lesser note, it has generally been assumed that the dose-response relationship for active smokers is reasonably well characterized. Recent literature raises some questions on this issue [Moolgavkar et al., 1989; Gaffney and Altshuler, 1988; Freedman and Navidi, 1987a,b; Whittemore, 1988].)

Citing cigarette-equivalents calculated in other sources, Vutuc (1984) assumes a range of 0.1 to 1.0 cigarettes per day for ETS exposure. Relative risks for nonsmokers are calculated for 10-year age intervals (40 to 80) based on the reported relationships of dose, time, and lung cancer incidence in Doll and Peto (1978). Relative risks for smokers of 0.1 to 1.0 cigarettes per day give a range in relative risk from 1.03 to 1.36. The author concludes that "as it applies to passive

smokers, this range of exposures may be neglected because it has no major effect on lung cancer incidence." Vutuc assumes that his figures apply to both males and females. If an exposure fraction of 75% is assumed for both males and females, the range of relative risks given correspond to a range for population-attributable risk. If the number of LCDs among never-smokers in the United States in 1988 is about 6,500 females and 3,000 males (personal communication from the American Cancer Society), then the number of LCDs in never-smokers attributable to ETS is estimated to range from 240 to 2,020 (140 to 1,380 for females alone). So Vutuc's figures are consistent with several hundred excess LCDs among never-smokers in the United States. These estimates are from our extension of Vutuc's analysis, however, and are not the claim of the author.

Repace and Lowrey (1985) describe a cigarette-equivalents approach as an alternative to their "phenomenological" approach discussed in Section 6.2.1. One objective is to provide an assessment of exposure to ETS from all sources that is more inclusive and quantitative than might be available from studies based on spousal smoking. They consider exposure to ETS both at home and in the workplace, using a probability-weighted average of exposure to respirable suspended particulates (RSP) in the two environments. Exposure values are derived from their basic equilibrium model relating ambient concentration of particulates to the number of burning cigarettes per unit volume of air space and to the air change rate. From 1982 statistics of lung cancer mortality rates among smokers and their own previous estimates of daily tar intake by smokers, the authors calculate a lung cancer risk for active smokers of 5.8×10^{-6} LCDs/year per mg tar/day per smoker of lung cancer age. The essential assumption linking lung cancer risk in passive and active smokers is that inhaled tobacco tar poses the same risk to either on a per unit basis. Extrapolation of risk from exposure levels for active smokers to values calculated for passive smokers is accomplished by assuming that dose-response follows the one-hit model for carcinogenesis. An estimated 555 LCDs per year in U.S. nonsmokers (never-smokers and former smokers) are attributed to ETS exposure (for 1980). The ratio of total LCDs in 1988 to 1980 is approximately 1.37 (Repace, 1989). With that population adjustment factor, the approximate number of LCDs attributable to ETS among nonsmokers is closer to 760 for 1988 (including former smokers).

Method 3 of Robins (NRC, 1986, Appendix D--again, included in the NRC report but not specifically endorsed by the committee) extrapolates from data on active smoking, along with several assumptions. Applying his results to 6,500 females and 3,000 males, the range of excess LCDs in never-smokers due to ETS is 550 to 2,940 for females and 153 to 1,090 for males.

Russell and coworkers (1986) use data on urinary nicotine concentrations in smokers and nonsmokers to estimate exposure and risk from passive smoking. The risk of premature death

from passive smoking is presumed to be in the same ratio to premature death in active smokers as the ratio of concentrations of urinary nicotine in passive to active smokers (about 0.007). Calculations are made using vital statistics for Great Britain and then extrapolated to the United States. The latter estimate, 4,000+ deaths per year due to passive smoking, is for all causes of death, not just LCDs.

Arundel et al. (1987) attributes only five LCDs among female never-smokers to ETS exposure. The corresponding figure for males is seven (both figures are adjusted to 6,500 females and 3,000 males). The expected lung cancer risk for never-smokers is estimated by downward extrapolation of the lung cancer risk per mg of particulate ETS exposure for current smokers. The authors' premise is that the lung carcinogenicity of ETS is entirely attributable to the particulate phase of ETS, and the consequent risk in passive smoking is comparable to active smoking on a per mg basis of particulate ETS retained in the lung. If the vapor phase of ETS were also considered, the number of LCDs attributable to ETS would likely increase (e.g., see Wells, 1991).

6.3. THIS REPORT'S ESTIMATES OF LUNG CANCER MORTALITY ATTRIBUTABLE TO ETS IN THE UNITED STATES

6.3.1. Introduction and Background

This report uses the epidemiologic approach because of the abundance of human data from actual environmental exposures. Furthermore, the assumptions are fewer and more valid than for the cigarette-equivalents approach. The report generally follows the epidemiologic methodology used by the NRC (NRC, 1986) and others (Section 6.2.1), with three important differences. The first difference is that the NRC combined the data on females and males for its summary relative risk estimate. This report uses only the data on females because there are likely to be true sex-based differences in relative risk due to differences in exposure to background ETS and differences in background (i.e., non-tobacco-smoke-related) lung cancer risk. Furthermore, the vast majority of the data are for females. The second difference is that the NRC combined study estimates of relative risk across countries for its summary relative risk estimate; this report combines relative risk estimates only within countries, and then bases the U.S. population risk assessment on the U.S. estimate only. As discussed in Chapter 5, there are apparently true differences in the observed relative risk estimates from different countries, which might reflect lifestyle differences, differences in background lung cancer rates in females, exposure to other indoor air pollutants, and differences in exposure to background levels of ETS. Therefore, for the purposes of U.S. population risk assessment, it is appropriate to use the U.S. studies; in addition, far more studies are currently available so there is less need to combine across countries. The

third difference is that the NRC corrected its overall estimate of relative risk downward for smoker misclassification bias. In this report, the individual study estimates are corrected for smoker misclassification bias at the outset, i.e., prior to any analysis, using the particular parameters appropriate for each separate study (Appendix B).

The basic NRC model is defined as

$$RR(d_E) = (1 + Z * \beta d_N)/(1 + \beta d_N)$$

where $RR(d_E)$ is the relative risk for the group of never-smokers identified as "exposed" to spousal ETS (plus background ETS) compared with the group identified as "unexposed" (but actually exposed to background ETS); Z is the ratio between the operative mean dose level in the exposed group, d_E, and the mean dose level in the unexposed group, d_N; and β is the amount of increased risk per unit dose. The equation is only defined for $Z > RR(d_E) > 1$ (see Section 8.3).

The method used here is based on several assumptions: (1) that body cotinine levels in never-smokers are linearly related to ETS exposure; (2) that current ETS exposure is representative of past exposures; and (3) that the excess risk of lung cancer in nonsmokers exposed to ETS is linearly related to the dose absorbed.

Estimates of $RR(d_E)$ for female never-smokers were derived in Chapter 5, where they were corrected for smoker misclassification bias; these are redefined in Section 6.3.2 as RR_2. The relative risk estimates are then adjusted to be applicable to different baseline exposure groups in order to calculate population risks for never-smoking women. In order to extend the analyses to female former smokers and male never- and former smokers, the relative risks are converted to excess or additive risks. The use of additive risks is more appropriate for these groups because of the different baseline lung cancer mortality rates by sex and smoking status (former vs. never).

More specifically, estimates of ETS-attributable population mortality are calculated from female lung cancer mortality rates, which are themselves derived from summary relative risk estimates either from the 11 U.S. studies combined (Section 6.3.3) or from the Fontham et al. (1991) study alone (Section 6.3.4), along with other parameter estimates from prominent sources (Section 6.3.2). The LCMRs in this instance are defined as the number of LCDs in 1985 per 100,000 of the population at risk. The LCMR in U.S. women under age 35 is minuscule, so only persons of age 35 and above are considered at risk. Although these LCMRs are expressed as a mortality rate per 100,000 of the population at risk, as derived they are applicable only to the entire population at risk and not to any fraction thereof that might, for example, have a different average exposure or age distribution.

The LCMR for the subpopulation and exposure scenario to which the epidemiologic studies apply most directly--never-smoking females exposed to spousal ETS--is estimated first. That estimate is then incremented to include exposure to nonspousal ETS for all never-smoking females. For the ETS-attributable population mortality estimates, these LCMRs are applied to never-smoking males and former smokers at risk, as well as to the females at risk for which the rates were specifically derived. The most reliable component of the total estimate constructed for the United States is the estimate for the female never-smokers exposed to spousal ETS. The other components require additional assumptions, which are described. As the number of assumptions increases, so does the uncertainty of the estimates. Thus, the total estimate of lung cancer risk to U.S. nonsmokers of both sexes is composed of component estimates of varying degrees of certainty.

One might argue that smokers are among those most heavily exposed to ETS, since they are in close proximity to sidestream smoke (the main component of ETS) from their own cigarettes and are also more likely than never-smokers to be exposed to ETS from other smokers. The purpose of this report, however, is to address respiratory health risks from ETS exposure in nonsmokers. In current smokers, the added risk from passive smoking is relatively insignificant compared to the self-inflicted risk from active smoking.

6.3.2. Parameters and Formulae for Attributable Risk

Several parameters and formulae are needed to calculate attributable risk. These are presented in Table 6-1, with the derivations explained below.

The size of the target population, in this case the number of women in the United States of age 35+ in 1985, is denoted by N, with $N = N_1 + N_2$, where N_1 = the number of ever-smokers and N_2 = the number of never-smokers. The total number of LCDs from all sources, T, is apportioned into components from four attributable sources: (1) non-tobacco-smoke-related causes, the background causes that would persist in an environment free of tobacco smoke; (2) background ETS, which refers to all ETS exposure other than that from spousal smoking; (3) spousal ETS; and (4) ever-smoking. The risk from non-tobacco-smoke-related causes (source 1) is a baseline risk (discussed below) assumed to apply equally to the entire target population (never-smokers and ever-smokers alike). The ever-smoking component of attributable risk (source 4) refers to the incremental risk above the baseline in ever-smokers (this report does not partition the incremental risk in ever-smokers further into components due to background ETS and spousal ETS, except for long-term [5+ years] former smokers). The background ETS component (source 2) is the incremental risk above the baseline in all never-smokers from exposure to nonspousal sources of

Table 6-1. Definition and estimates of relative risk of lung cancer for 11 U.S. studies combined for various exposure sources and baselines; population parameter definitions and estimates used to calculate U.S. population-attributable risk estimates for ETS

DENOMINATOR (Baseline)	NUMERATOR of relative risk			
	All persons	Never-smokers ETS exposure		Current and former smokers
Source of exposure	Non-tobacco-smoke sources of exposure	Background ETS	Background ETS and spousal ETS	Active smoking
	[nt]	[nt]+[ETS_B]	[nt]+[ETS_B]+[ETS_S]	[nt]+[ETS]+[ACT]
[nt]	1	RR_{03} = 1.34	RR_{02} = 1.59[1]	RR_{01} = 13.8
[nt]+[ETS_B]	-	-	RR_2 = 1.19[2]	RR_{11} = 10.3
[nt]+[ETS_B]+[ETS_S]	-	-	-	RR_1 = 9.26[3]

[1]Basic adjustment for background exposure with Z = 1.75.
[2]Pooled value from 11 U.S. studies for never-smoking females.
[3]RR_1 = a weighted average of 11.94 for women active smokers (63.4%) and 4.69 for women former smokers (36.6%) = 9.26.

Definitions and Estimates of Population Parameter Values

N = Total number of women in U.S. (1985) age 35+ = N_1 (ever-smokers) + N_2 (never-smokers) = 25.7 million + 32.3 million = 58 million.
P_1 = Prevalence (proportion) of female ever smokers age 35+ = 0.443.
P_2 = Proportion of NS women exposed to equivalent spousal ETS (plus background ETS) = 0.6.
Z = Ratio of body cotinine levels in (nonsmokers exposed to background ETS plus spousal ETS) to (nonsmokers exposed to background ETS only) = 1.75.
T = Total LCDs in United States in 1985 among women aged 35+ = 38,000.

ETS. The spousal ETS component (source 3) is the additional incremental risk in never-smokers exposed to spousal smoking.

The calculational formulae also require values for the parameters P_1 (prevalence of ever-smokers), P_2 (proportion of never-smokers exposed to spousal smoking), RR_1 (average lung cancer risk for ever-smokers relative to the average risk for never-smokers in the population), and RR_2 (lung cancer risk of never-smokers exposed to spousal ETS relative to never-smokers not exposed to spousal ETS). Additional parameters (RR_{11}, Z, RR_{01}, RR_{02}, and RR_{03}) are introduced or developed below.

The "baseline" risk is defined as the term in the denominator of a risk ratio. For example, in RR_1 the baseline risk is the lung cancer risk in a population of never-smokers with P_2 exposed to spousal ETS and $1 - P_2$ not exposed to spousal ETS. The conversion of RR_1 to the same baseline risk as RR_2 (the risk of never-smokers not exposed to spousal ETS but still exposed to non-tobacco-smoke-related causes and to background ETS), is given by

$$RR_{11} = RR_1(P_2RR_2 + 1 - P_2). \quad (6\text{-}1)$$

To convert relative risks to the baseline risk of lung cancer from non-tobacco-smoke-related causes only (i.e., excluding background ETS in the baseline) requires some assumptions. Let RR_{02} denote the conversion of RR_2 to this new baseline. It is assumed that: (1) the excess risk of lung cancer from ETS exposure is proportional to ETS exposure; and (2) the ratio of ETS exposure from spousal smoking plus other sources to exposure from other sources alone, denoted by Z, is known and $Z > RR_2 > 1$. (For the values used in this report, this relation is true. See also the discussion in Section 8.3.) Under these assumptions, $RR_{02} = 1 + \beta Z d_N$ (from Section 6.3.1), or

$$RR_{02} = (Z - 1)/(Z/RR_2 - 1). \quad (6\text{-}2)$$

Determination of a value for Z from data on cotinine concentrations (or cotinine/creatinine) is discussed below. The conversion of RR_1 to the same zero-ETS baseline risk as RR_{02} follows from multiplying expression (6-1) by RR_{02}/RR_2, i.e.,

$$RR_{01} = RR_1(P_2RR_{02} + (1 - P_2)RR_{02}/RR_2). \quad (6\text{-}3)$$

The terms RR_{01} and RR_{02} are the lung cancer risks for ever-smokers and for never-smokers exposed to spousal ETS, respectively, relative to the risk for never-smokers in a zero-ETS

environment. The risk of never-smokers not exposed to spousal ETS (but exposed to background ETS and nonsmoking causes) relative to the zero-ETS baseline risk is

$$RR_{03} = RR_{02}/RR_2. \quad (6\text{-}4)$$

The population-attributable risk of lung cancer in the total population for a source (risk factor) is a ratio. The numerators of the ratios for sources of tobacco smoke are:

current/former active smoking in ever-smokers,
$P_1(RR_{01} - 1)$; (6-5)

background ETS plus spousal ETS in never-smokers exposed to both,
$(1 - P_1)P_2(RR_{02} - 1)$; and (6-6)

background ETS in never-smokers not exposed to spousal ETS,
$(1 - P_1)(1 - P_2)(RR_{02}/RR_2 - 1)$. (6-7)

The denominator for each term is their sum plus one, i.e.,

$$Ex(6\text{-}5) + Ex(6\text{-}6) + Ex(6\text{-}7) + 1 \quad (6\text{-}8)$$

where Ex(6-5) refers to expression (6-5), etc. The population-attributable risk for remaining causes of lung cancer (non-tobacco-smoke-related background causes) is

$$1/Ex(6\text{-}8). \quad (6\text{-}9)$$

Multiplying the population-attributable risk for a source by the total number of LCDs yields the number of LCDs attributable to that source. An alternative and equivalent derivation of the source-attributable LCD estimates can be performed by first calculating LCMRs. LCMRs are obtained for each source as follows:

non-tobacco-smoke-related causes:	$LCMR_{nt} = 10^5 Ex(6\text{-}9)T/N.$
ever-smoking:	$LCMR_{nt}(RR_{01} - 1).$
spousal ETS:	$LCMR_{nt}(RR_{02} - RR_{03}).$
background ETS:	$LCMR_{nt}(RR_{03} - 1).$

Then the number of LCDs attributable to a source is estimated by multiplying the LCMR for that source by the total population at risk from that source.

We now consider parameter values for N, T, P_1, P_2, RR_1, and Z to be used with the value 1.19 for RR_2, the pooled estimate of RR_2 from the 11 U.S. studies (Table 5-17), for the population risk assessment in Section 6.3.3. The value used for RR_2 is then changed to 1.28, the estimate from the Fontham et al. (1991) study in the United States, and a new value of Z is constructed from the cotinine data in that study for the alternative population risk assessment calculations in Section 6.3.4. The female population in 1985 of age 18+ years of age is approximately 92 million (U.S. DHHS, 1989, Chapter 3). Detailed census data by age for 1988 indicate that the proportion of women 35+ years of age in the female population of age 18+ is 0.63 (U.S. Bureau of the Census, 1990). Applying that proportion to the 1985 population gives approximately 58 million women of aged 35+ in 1985, the value used for N. There were approximately 38,000 female LCDs in the United States in 1985 (U.S. DHHS, 1989), which is used as the value for T.

Using figures from the Bureau of the Census and the 1979/80 National Health Interview Survey, Arundel et al. (1987) estimate the number of women of age 35+ by smoking status, obtaining a value of 0.443 as the fraction of ever-smokers. The National Center for Health Statistics (as reported in U.S. DHHS, 1989) provides the proportion of the female population by smoking status (never, former, current) for 1987. When applied to figures from the Bureau of the Census (1990) for the female population by age group available for 1988, the same fractional value (0.443) is obtained. These sources suggest that the proportion of ever-smokers in the female population has been fairly constant between 1980 and 1987, so P_1 will be given the value 0.443. Multiplying N by P_1 gives an estimate of $N_1 = 25.7$ million ever-smokers, leaving $N_2 = 32.3$ million never-smokers.

RR_1 applies to ever-smokers, which consist of current and former smokers. The relative risks of current and former female smokers of age 35+ for the period 1982-1986 are estimated at 11.94 and 4.69, respectively, from data in the American Cancer Society's Cancer Prevention Study II (CPS-II; as reported in U.S. DHHS, 1989). For 1985, the composition of ever-smokers is 63.4% current smokers and 36.6% former smokers (CDC, 1989a). Using those percentages to weight the relative risks for ever-smokers and former smokers gives 9.26, which will be used as the value of RR_1.

The proportion of never-smokers exposed to spousal ETS in epidemiologic studies typically refers to married persons, so we need to consider how to treat unmarried persons as well in order to set a value for P_2. The American Cancer Society's CPS-II (reported in Stellman and Garfinkel, 1986) percentages for marital status of all women surveyed (not just never-smokers) are: married, 75.3; divorced, 5.1; widowed, 14.6; separated, 0.8; and single, 4.2. Our estimates of risk apply to married female never-smokers, which comprise about 75% of female never-smokers,

so it is necessary to consider exposure to ETS in the remaining 25% of unmarried female never-smokers.

Cummings (1990) obtained urinary cotinine levels on a total of 663 self-reported never-smokers and former smokers. The cotinine levels were slightly higher in males than in females (9.6 and 8.2 ng/mL, respectively), and slightly more than one-half of the subjects were females. The average cotinine level was 10.7 ng/mL for married subjects if the spouse smoked and 7.6 ng/mL otherwise. The average cotinine levels reported by marital status are: married, 8.3 ng/mL; never married, 10.3 ng/mL; separated, 11.8 ng/mL; widowed, 10.4 ng/mL; and divorced, 9.2 ng/mL. The study, in which 7% of the subjects were of age 18 to 29, and 47% were of age 60 to 84, does not claim to be representative. Nevertheless, the results suggest that in terms of ETS exposure, an unmarried never-smoker is probably closer, on average, to a never-smoker married to a smoker (an exposed person) than to a never-smoker married to a nonsmoker (an unexposed person). This observation is also consistent with the findings of Friedman et al. (1983).

The proportion of never-smoking controls exposed to spousal smoking varies among studies in the United States. If we exclude studies of uncertain representativeness, the median value for the remaining studies is 0.6. From the evidence on ETS exposure to unmarried female never-smokers, it is reasonable to assume that their exposure to ETS, on average, is at least as large as the average background level plus 60% of the average exposure from spousal smoking. For the calculations needed from these figures, this assumption is equivalent to treating unmarried and married female never-smokers alike in terms of exposure to ETS (i.e., 60% exposed at a level equivalent to spousal smoking plus background and 40% exposed at the background level only). Consequently, the value $P_2 = 0.6$ is assumed to apply equally to married and unmarried female never-smokers.

The NRC report of 1986 uses $Z = 3$ for the ratio of ETS exposure from spousal smoking plus other sources to ETS exposure from nonspousal sources alone. That value was primarily based on data from Wald and Ritchie (1984), for men in Great Britain, although Lee (1987b) had reported a value of 3.3 for women in Great Britain. The results of Coultas et al. (1987) also were considered, wherein a value of 2.35 was observed for saliva cotinine levels in a population-based survey of Hispanic subjects in New Mexico. More recent data suggest that a lower value of Z may be more accurate for the United States. The study of 663 volunteers in Buffalo, New York, reported by Cummings et al. (1990), observed a value of 1.55 based on mean urinary cotinine levels among married females ($n = 225$; Cummings, 1990). A study by Wall et al. (1988) containing 48 nonsmokers observed a ratio of mean cotinine levels of 1.53. A survey of municipal workers at a health fair found a cotinine ratio of 2.48 for the 112 women surveyed, but the comparison is between women who shared living quarters with a smoker and those who did not

(Haley et al., 1989). The 10-country collaborative cotinine study conducted by IARC (Riboli et al., 1990) collected urinary cotinine samples from nonsmoking women in four groups totaling about 100 each--married to a smoker (yes, no) and employed (yes, no)--including two locations, Los Angeles and New Orleans, in the continental United States. The ratios of average cotinine/creatinine concentrations for women married to a smoker to women not married to a smoker range from 1.75 to 1.89 in New Orleans, when the percentage of women employed is assumed to be between 25% and 75%. The data from Los Angeles contain an abnormally high mean for women who are employed and also married to a smoker (a mean of 14.6 based on only 13 observations, compared to the other three means for Los Angeles of 2.1, 4.5, and 6.6), so only the two means for unemployed women (married to a smoker and married to a nonsmoker) were used. The resultant ratio of cotinine/creatinine concentrations is 1.45. Data from the Fontham et al. (1991) study of lung cancer and ETS exposure in five U.S. cities yield a Z of 2.0 based on mean urinary cotinine levels in 239 never-smoking women (data provided by Dr. Elizabeth Fontham).

Cotinine data exhibit variability both within and between subjects, as well as between studies due to different experimental designs, protocols, and geographical locations (see also Chapter 3). Most of the Z values from recent U.S. studies range between 1.55 and 2.0. A value of 1.75 for Z appears reasonable based on the available U.S. data and will be used in Section 6.3.3 along with the combined RR estimate from 11 U.S. studies (Chapter 5) to calculate ETS-attributable lung cancer mortality estimates. Z = 2.0 and Z = 2.6, which are based on *median* cotinine levels, will be used in Section 6.3.4 for alternative calculations of lung cancer mortality based on the results of the Fontham et al. (1991) study. The sensitivity of the lung cancer mortality estimates to changes in Z and other parameters is discussed in Section 6.3.5.

6.3.3. U.S. Lung Cancer Mortality Estimates Based on Results of Combined Estimates from 11 U.S. Studies

This section calculates ETS-attributable U.S. lung cancer mortality estimates based on the combined relative risk estimate (RR_2 = 1.19) derived in Chapter 5 for the 11 U.S. studies. Alternatively, the estimate from just the combined Tier 1 and Tier 2 studies (RR_2 = 1.22 from 8 of the 11; see Table 5-17) could have been used because these eight studies were assessed as having the greater utility in terms of evaluating the lung cancer risks from ETS; however, the results would be virtually the same because the relative risk estimates are so similar. It was therefore decided to use the data from all the U.S. studies for the purposes of the population risk assessment.

6.3.3.1. *U.S. Lung Cancer Mortality Estimates for Female Never-Smokers*

The parameter values presented in Section 6.3.2 are assumed along with $RR_2 = 1.19$. For $Z = 1.75$, $RR_{02} = 1.59$ (from expression 6-2, denoted hereafter as Ex(6-2); see also Table 6-1). Given those parameter values, the formulae in Section 6.3.2 yield the estimated lung cancer mortality for U.S. women in 1985 by smoking status (ever-smoker, never-smoker exposed to spousal ETS, and never-smoker not exposed to spousal ETS) and source (non-tobacco-smoke-related causes, background ETS in never-smokers, spousal ETS in never-smokers, and ever-smoking), as displayed in Table 6-2. The LCMR from non-tobacco-smoke-related causes ($LCMR_{nt}$) is estimated to be 9.4 per 100,000 and is assumed to apply equally to all persons in the target population, regardless of smoking status. The excess LCMR in never-smokers from exposure to background ETS is 3.2, with an additional 2.4 if exposed to spousal ETS. The excess LCMR in ever-smokers, which includes whatever effect exposure to ETS has on ever-smokers as well as the effect from active smoking, is 120.8.

In rounded figures, 5,470 (14.4%) of the 38,000 LCDs in U.S. women age 35 and over in 1985 are unrelated to smoking (active or passive). The remaining 32,530 LCDs (85.6% of the total) are attributable to tobacco smoke: 31,030 in 25.7 million ever-smokers and 1,500 in 32.3 million never-smokers. These 1,500 ETS-attributable LCDs in never-smokers account for about one-third of all LCDs in female never-smokers. Of the 1,500 LCDs, about 1,030 (69%) are due to background ETS, and 470 (31%) are from spousal ETS. In summary, the total 38,000 LCDs from all causes is due to non-tobacco-smoke-related causes, 5,470 (14.4%), occurring in ever-smokers and never-smokers; ever-smoking, i.e., the effects of past and current active smoking as well as ETS exposure, 31,030 (81.7%), occurring in ever-smokers; and background ETS, 1,030 (2.7%), and spousal ETS, 470 (1.2%), occurring in never-smokers. In other words, ever-smoking causes about 81.7% of the lung cancers in women age 35 and over; exposure to ETS from all sources accounts for some 3.9%; and causes unrelated to tobacco smoke are responsible for the remaining 14.4%. The LCDs in never-smokers attributable to ETS equal about 5% (1,500/31,030) of the total attributable to ever-smoking. Part of the mortality attributed to ever-smoking here, however, is due to ETS exposure in former smokers, to be taken into account in Section 6.3.3.3.

6.3.3.2. *U.S. Lung Cancer Mortality Estimates for Male Never-Smokers*

There are 11 studies worldwide of exposure to ETS and lung cancer in males. The studies and their respective relative risks are AKIB, 1.8; BROW, 2.2; BUFF, 33+ years' exposure, 1.6; CORR, 2.0; HUMB, 4.2; KABA, 1.0; LEE, 1.3; HIRA(Coh), 2.25; HOLE(Coh), 3.5; plus the data in Kabat (1990), 1.2; and Varela (1987, Table 13 scaled down to 50 years of exposure), 1.2. (Data

Table 6-2. Estimated female lung cancer mortality by attributable sources for United States, 1985, using the pooled relative risk estimate from 11 U.S. studies[1]

			Lung cancer mortality[2]				
		(1)	(2)	(3)	(4)	(5)	
Smoking status[3]	Exposed to spousal ETS	Number at risk (in millions)	Non-tobacco-smoke-related causes[4]	Background ETS	Spousal ETS	Ever-smoking	Total
NS	No	12.92	1,220 (3.2)	410 (1.1)			
NS	Yes	19.38	1,830 (4.8)	620 (1.6)	470 (1.2)		
ES		25.69	2,420 (6.4)			31,030[5] (81.7)	
Total		58.00	5,470 (14.4)	1,030 (2.7)	470 (1.2)	31,030 (81.7)	38,000

[1]Percentage of grand total (38,000) in parentheses.

[2]The nonblank entries in the table are the product of an individual's attributable risk of lung cancer from non-tobacco-smoke-related causes (expression 6-9 (38,000/58,000,000)), the number at risk in column (1), and the following column-specific multiples: Col. (2) 1
Col. (3) $RR_{03} - 1$
Col. (4) $RR_{02} - RR_{03}$
Col. (5) $RR_{01} - 1$

[3]NS = never-smokers; ES = ever-smokers.

[4]Background sources in the absence of tobacco smoke (i.e., in a zero-ETS environment).

[5]This figure attributes all lung cancer in ever-smokers above the background non-tobacco-smoke-related rate to ever-smoking.

for BROW, BUFF, and HUMB were supplied via personal communication from Drs. Brownson, Buffler, and Humble.) A weighted average of the passive smoking risk (RR_2) from these 11 studies is about 1.6. For the seven U.S. studies, BROW, BUFF, CORR, HUMB, KABA, Kabat (1990), and Varela (1987), the weighted average RR is about 1.4, but this value is heavily weighted (about 66%) by the Kabat (1990) and Varela (1987) studies, neither of which was used in the analysis of the female data. The combined risk for the five U.S. studies not including Kabat (1990) and Varela (1987) is about 1.8, but they are all small, low-weight studies. In any case, the observed relative risks for males appear to be at least as great as those for females.

When an attempt is made to correct the observed male risks for smoker misclassification, however, using the procedures outlined in Appendix B and the community survey-based misclassification factors for males (1.6% for current regular smokers, 15% for current occasional smokers, and 5.9% for former smokers), it is found that for most of these cohorts, the number of smokers misclassified as never-smokers either exceeds the relatively small number of observed never-smokers or is so great as to drive the corrected relative risk substantially below unity. This implies that the misclassification factors from the community surveys are too high to accurately correct the risks in the epidemiologic studies. Until better misclassification data on males are available, no real sense can be made of the male passive smoking relative risks.

Given the greater stability of the more extensive database on females, it was decided to apply the incremental LCMRs for spousal and nonspousal ETS exposure in female never-smokers to male never-smokers. The incremental LCMRs were used instead of the relative risk estimates because relative risk depends on the background risk of lung cancer (from non-tobacco-related causes) as well as the risk from ETS, and background lung cancer risk may differ between females and males. From Section 6.3.3.1, the LCMR from spousal ETS exposure was 2.4 per 100,000 at risk, and the LCMR from nonspousal ETS exposure was 3.2 per 100,000. The 1985 male population age 35 and over is 48 million (U.S. DHHS, 1989), of whom 27.2% (private communication from Dr. Ronald W. Wilson of the U.S. National Center for Health Statistics), or 13.06 million, were never-smokers. Of these, 24% (Wells, 1988), or 3.13 million, were spousally exposed. Applying the female ETS LCMRs, 3.13 million $\times$ 2.4/100,000 = 80 deaths in males from spousal ETS exposure and 13.06 million $\times$ 3.2/100,000 = 420 deaths from nonspousal exposure, for a total of 500 ETS-attributable LCDs among never-smoking males. These estimates based on female LCMRs are believed to be conservatively low because males generally have higher exposure to background ETS than females. This would lead to lower Z values and subsequently higher estimates of deaths attributable to background (nonspousal) ETS sources. In conclusion, confidence in these estimates for male never-smokers is not as high as those for female never-smokers.

6.3.3.3. *U.S. Lung Cancer Mortality Estimates for Long-Term (5+ Years) Former Smokers*

Because the risk of lung cancer from active smoking decreases with the number of years since smoking cessation (Section 4.2.2), passive smoking may be a significant source of lung cancer risk in long-term former smokers. There is, however, a scarcity of data on the relative risks of lung cancer for former smokers exposed to ETS. With former smokers, it is unknown how much of the observed lung cancer mortality is attributable to non-tobacco-smoke-related causes, how much is due to ETS exposure, and how much is accounted for by prior smoking. Consequently, neither the observational data on the number of lung cancers in the former smokers nor the relative risk data from never-smoking females are utilized. Instead, long-term former smokers are assumed to have the same LCMR from exposure to ETS as never-smoking females, as was assumed above for never-smoking males. In this manner, the lung cancer risk from ETS exposure can be calculated as an additional risk, supplemental to any remaining risk from previous active smoking. There is some uncertainty in the application of this assumption because the additional risk to long-term former smokers from ETS exposure may not, in fact, be the same as the risk to never-smokers. For example, ETS may have a greater promotional effect on former smokers because of their previous exposures to high concentrations of carcinogens from active smoking.

Female ever-smokers comprise about 44.3%, or 25.7 million, of the total U.S. female population age 35 and over of 58 million. Long-term (5+ years) former smokers comprise about 34% of these ever-smokers (U.S. DHHS, 1990b), or about 8.7 million women. Using a 2.2 concordance factor for former smokers married to ever-smokers versus never-smokers married to never-smokers (see Appendix B), it is estimated that about 77% of the former smokers, or about 6.7 million, would be spousally exposed compared with the 60% for the never-smokers. Thus, based on the LCMRs derived for female never-smokers, the expected number of ETS-attributable LCDs for female long-term former smokers would be 6.7 million × 2.40/100,000 = 160 deaths from spousal exposure and 8.7 million × 3.20/100,000 = 280 deaths from nonspousal exposure, for a total of 440.

Male ever-smokers comprise 72.8% of the U.S. male population, age 35 and over, of 48 million, equal to 35 million; of these, about 43% (derived from data in U.S. DHHS, 1990b, page 60, Table 5), or about 15 million, are 5+ year quitters. Of the never-smoking males, 24% were married to smokers (Section 6.3.3.2). Again using a 2.2 concordance factor for former smokers, it is estimated that 41% of the 15 million former smoking males, or 6.2 million, would be married to ever-smokers. Applying the female never-smoker LCMRs from Section 6.3.3.1, 6.2 million × 2.40/100,000 = 150 deaths from spousal ETS exposure and 15 million × 3.20/100,000 = 480 deaths

from nonspousal ETS exposure for a total of 630 ETS-attributable LCDs among male long-term former smokers.

Table 6-3 displays the resultant estimates for LCDs attributable to background ETS and spousal ETS by sex for never-smokers and for former smokers who have quit for at least 5 years. The LCMRs for background ETS and spousal ETS, assumed to be independent of smoking status and sex, are the same as derived in Section 6.3.3.1 for female never-smokers (3.2 and 2.4, respectively). Background ETS accounts for about 2,200 (72%) and spousal ETS for 860 (28%) of the total due to ETS. Of the 3,060 ETS-attributable LCDs, about two-thirds are in females (1,930, 63%) and one-third in males (1,130, 37%). More females are estimated to be affected because there are more female than male never-smokers. By smoking status, two-thirds are in never-smokers (2,000, 65%) and one-third in former smokers who have quit for at least 5 years (1,060, 35%).

The numbers shown in Table 6-3 depend, of course, on the parameter values assumed for the calculations. The sensitivity of the totals in Table 6-3 to alternative parameter values is addressed in Section 6.3.5. First, however, tables equivalent to Tables 6-2 and 6-3 are developed based on the FONT study alone for comparison.

6.3.4. U.S. Lung Cancer Mortality Estimates Based on Results of the Fontham et al. (1991) Study (FONT)

The estimate of RR_2 (1.19), the risk of lung cancer to female never-smokers with spousal ETS exposure relative to the risk for female never-smokers without spousal ETS exposure, used in Section 6.3.3, is based on the combined outcomes of the 11 U.S. epidemiologic studies from Chapter 5 (see Table 5-17). In this section, the quantitative population impact assessment is repeated with FONT, the single U.S. study with Tier 1 classification (Section 5.4.4), as the source of the estimates of RR_2 and Z (constructed from urine cotinine measures), with the remaining parameter values left unchanged. While a single study has lower power and larger confidence intervals on the relative risk estimate than can be obtained by combining the various U.S. studies, using the specific data from a single study decreases the uncertainties inherent in combining results from studies that are not fully comparable. **FONT is the only study of passive smoking and lung cancer that collected cotinine measurements, thus providing estimates for RR_2 and Z from a single study population.** The total number of lung cancers attributable to total ETS exposure is particularly sensitive to those two parameters (discussed in Section 6.3.5).

The NCI-funded Fontham et al. study (1991) is a large, well-conducted study designed specifically to investigate lung cancer risks from ETS exposure (see also the critical review in

Table 6-3. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using 11 U.S. studies (never-smokers and former smokers who have quit 5+ years)[1]

Smoking status[2]	Sex	Exposed to spousal ETS	(1) Number at risk (in millions)	Lung cancer mortality (2) Background ETS	(3) Spousal ETS	(4) Total ETS	Total ETS by sex and smoking status
NS	F	No	12.92	410		410	
NS	F	Yes	19.38	620	470	1,090	1,500 (NS,F)
NS	M	No	9.93	320		320	
NS	M	Yes	3.13	100	80	180	500 (NS,M)
FS	F	No	2.0	60		60	
FS	F	Yes	6.7	210	160	370	430 (FS,F)
FS	M	No	8.8	280		280	
FS	M	Yes	6.2	200	150	350	630 (FS,M)
Total			69.07	2,200 (71.9)	860 (28.1)	3,060	3,060

[1]Percentage of total ETS-attributable lung cancer deaths (3,060) in parentheses.
[2]NS = never-smokers; FS = former smokers who have quit 5+ years ago.

Appendix A). It addresses some of the methodological issues that have been of concern in the interpretation of results regarding lung cancer and passive smoking: smoker misclassification, use of surrogate respondents, potential recall bias, histopathology of the lung tumors, and possible confounding by other factors (see also Sections 5.3, 5.4.2, and 5.4.3). Cases and controls were drawn from five major cities across the United States (Atlanta, New Orleans, Houston, Los Angeles, and San Francisco) and, hence, should be fairly representative of the general U.S. population, at least of urban areas with moderate climates. Furthermore, the results of the study are consistent across the five cities.

In spite of the care incorporated into the FONT design to avoid smoker misclassification bias, some might still exist; thus, the adjusted relative risk of 1.29 reported in FONT is "corrected" slightly to 1.28 in this report. The parameter P_2, the proportion of never-smokers exposed to spousal ETS, was assigned the value 0.60 in the preceding section. In FONT, the observed proportion of spousal-exposed controls is 0.60 (0.66) for spousal use of cigarettes only (any type of tobacco) among colon-cancer controls and 0.56 (0.63) in population controls. Consequently, the previous value of 0.60 is retained. Of the 669 FONT population controls, whose current cotinine levels are considered the most representative of typical ETS exposure, there were 59 living with a current smoker and 239 whose spouses never smoked. (The other 371 were nonsmoking women who either no longer lived with a smoking spouse or whose spouse was a former smoker.) The *mean* cotinine level for never-smoking women with spouses who are current smokers (n = 59) is 15.90 ± 16.46; the mean level for the other 239 was 7.97 (± 11.03). The ratio is 15.90/7.97, giving Z = 2.0 (data provided by Dr. Elizabeth Fontham). The median is a measure of central tendency that is less sensitive to extremes, so the ratio of *median* cotinine levels is also considered (Z = 11.4/4.4 = 2.6). Results for both values of Z are displayed in Tables 6-4 and 6-5, which correspond to Tables 6-2 and 6-3, respectively, of the previous sections for direct comparison.

The results of Section 6.3.2 are based on $RR_2 = 1.19$ (combined U.S. study results) and Z = 1.75 (from studies on cotinine levels). In this section, RR_2 and Z are both increased (RR_2 to 1.28 and Z to 2.0 and 2.6). Correcting $RR_2 = 1.28$ for background ETS exposure yields estimates of $RR_{02} = 1.78$ (i.e., the relative risk from spousal and background ETS) for Z = 2.0, and $RR_{02} = 1.55$ for Z = 2.6. The relative risk estimate from exposure to background ETS only becomes $RR_{03} = 1.39$ for Z = 2.0, and $RR_{03} = 1.21$ for Z = 2.6. The change in RR_2, from 1.19 to 1.28, increases the estimated number of LCDs from background and spousal ETS, whereas increasing Z decreases the figure for background ETS and has no effect on the number for spousal ETS (see Tables 6-2 and 6-4). Relative to the total ETS-attributable LCD estimate in the last section

Table 6-4. Female lung cancer mortality estimates by attributable sources for United States, 1985, using both the relative risk estimates and Z values from the Fontham et al. (1991) study[1]

			Lung cancer mortality[2]				
		(1)	(2)	(3)	(4)	(5)	
Smoking status[3]	Exposed to spousal ETS	Number at risk (in millions)	Non-tobacco-smoke-related causes[4]	Background ETS	Spousal ETS	Ever-smoking	Total
NS	No	12.92	1,120 (2.9) *1,280 (3.4)*	440 (1.2) *270 (0.7)*			
NS	Yes	19.38	1,680 (4.4) *1,920 (5.1)*	660 (1.7) *410 (1.1)*	660 (1.7) *660 (1.7)*		
ES		25.69	2,230 (5.9) *2,550 (6.7)*			31,220[5] (82.2) *30,900[5]* *(81.3)*	
Total		58.00	5,030 (13.2) *5,760 (15.2)*	1,100 (2.9) *680 (1.8)*	660 (1.7) *660 (1.7)*	31,220 (82.2) *30,900 (81.3)*	38,000

[1]Percentage of grand total (38,000) in parentheses. Calculations using Z = 2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z = 2.6 (ratio of median cotinine levels) are shown in italics.
[2]See Table 6-2 for formulae for table entries.
[3]NS = never-smokers; ES = ever-smokers.
[4]Baseline lung cancer mortality in the absence of tobacco smoke (i.e., in a zero-ETS environment).
[5]This figure attributes all lung cancer in ever-smokers above the non-tobacco-smoke-related rate to active smoking.

Table 6-5. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using the Fontham et al. (1991) study (never-smokers and former smokers who have quit 5+ years)[1,2]

Smoking status[3]	Sex	Exposed to spousal ETS	(1) Number at risk (in millions)	Lung cancer mortality (2) Background ETS	(3) Spousal ETS	(4) Total ETS	Total ETS by sex and smoking status
NS	F	No	12.92	440 *270*		440 *270*	1,760 *1,340* (NS,F)
NS	F	Yes	19.38	660 *410*	660 *660*	1,320 *1,070*	
NS	M	No	9.93	340 *210*		340 *210*	560 *390* (NS,M)
NS	M	Yes	3.13	110 *70*	110 *110*	220 *180*	
FS	F	No	2.0	70 *40*		70 *40*	530 *410* (FS,F)
FS	F	Yes	6.7	230 *140*	230 *230*	460 *370*	
FS	M	No	8.8	300 *190*		300 *190*	720 *530* (FS,M)
FS	M	Yes	6.2	210 *130*	210 *210*	420 *340*	
Total			69.07	2,360 (66.1) *1,460 (54.7)*	1,210 (33.9) *1,210 (45.3)*	3,570 *2,670*	3,570 *2,670*

[1]Calculations using Z = 2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z = 2.6 (ratio of median cotinine levels) are shown in italics.
[2]Percentage of total ETS-attributable lung cancer deaths (3,570; *2,670*) in parentheses.
[3]NS = never-smokers; FS = former smokers who have quit 5+ years ago.

(3,060), the net effect is an increase of 12% to 3,570 at Z = 2.0, and a decrease of 13% to 2,670 when Z = 2.6. (FONT is the largest study and therefore the dominant influence in the combined relative risk from the 11 U.S. studies [RR_2 = 1.19], so the outcomes being compared here with those in Section 6.3.3 are not independent. Similarly, the Z-value of 1.75 used with RR_2 = 1.19 in the first analysis is subjectively based on the outcomes of several U.S. cotinine studies, including the FONT cotinine results.) Overall, these two analyses support an estimate in the neighborhood of 3,000 total lung cancer deaths in never-smokers and former smokers (quitters of 5+ years) from exposure to ETS in the United States for 1985.

The 3,000 figure is a composite value from estimates of varying degrees of uncertainty. The confidence for the female never-smoker estimates is highest. The lung cancer estimates for never-smoking females from exposure to spousal ETS (470 to 660; from Tables 6-2 and 6-4) are based on the direct evidence from epidemiologic studies and require the fewest assumptions. Adding in a figure for exposure to background ETS in never-smoking females (680 to 1,100) is subject to the assumptions and other uncertainties attached to the estimate of the parameter Z. The relative risk from ETS exposure, which depends on the risk from background sources of lung cancer as well as the risk from ETS, may differ in females and males. Consequently, the absolute risk (LCMR) in never-smoking females was assumed to apply to never-smoking males, adding 390 to 560 to the total (80 to 110 for spousal ETS and 280 to 450 for background ETS; Tables 6-3 and 6-5). Males, however, are thought to have higher background exposures to ETS than females, so this assumption is likely to underestimate the ETS-attributable lung cancer mortality in males.

The confidence in the estimates for former smokers is less than in those for never-smokers. These estimates also are probably low because they assume that ETS-attributable rates in never-smokers and former smokers are the same. Figures for lung cancer mortality from ETS in former smokers, for the same categories as never-smokers (i.e., females and males, background and spousal ETS), account for an additional 940 to 1,250 (totals of 310 to 440 for spousal ETS and 500 to 810 for background ETS, for both sexes). These figures for former smokers are summed from appropriate entries in Tables 6-3 and 6-5 (Tables 6-2 and 6-4 do not make them explicit; they are accounted for in the entry for lung cancer attributable to ever-smoking).

Finally, there is statistical uncertainty in each of the LCD estimates resulting from sampling variations around all of the parameter estimates that were used in the calculations. It is already apparent that the estimate of total lung cancer mortality attributable to ETS is sensitive to the values of Z and RR_2. Uncertainties associated with the parameter values assumed and the sensitivity of the estimated total ETS-attributable LCDs to various parameter values are examined next.

6.3.5. Sensitivity to Parameter Values

The estimates for ETS-attributable lung cancer mortality are clearly sensitive to the studies, methodology, and choice of models used, and previous methodologies have been presented in Section 6.2. Even for this current model, however, estimates will vary with different input values. Specifically, the estimates depend on the parameter values assumed for the total number of lung cancer deaths from all sources (T), the population size (N), the proportion of ever-smokers in the population (P_1), the proportion of never-smokers exposed to spousal ETS (P_2), the risk of ever-smokers relative to never-smokers (RR_1), the risk of never-smokers exposed to spousal ETS relative to unexposed never-smokers (RR_2), and the ratio of ETS exposure from spousal smoking and background (i.e., nonspousal) sources to background sources alone (Z).

The effects of changing several of the parameters is readily discernible. A change in T/N produces a proportional change in the same direction for all estimates of attributable mortality. A change in P_1 creates a proportional change in the same direction in all mortality figures for ever-smokers and a change in the opposite direction proportional to $1 - P_1$ in all estimates for never-smokers. The parameter values assumed for these three parameters are from the sources described in the preceding text and are assumed to be acceptably accurate. The value of P_2 is assumed to be 0.6, but values between 0.5 and 0.7 are easily credible. At either of those extremes, there is a 17% change in the lung cancer mortality due to spousal smoking, which only amounts to 80 for the first analysis (Table 6-2) and 100 for the second one (Table 6-4). The impact of changing RR_1, RR_2, or Z on the total lung cancer mortality attributable to ETS from the first analysis is displayed in Table 6-6 for RR_1 from 8 to 11, for RR_2 between 1.04 and 1.35 (extremes of the 90% confidence intervals for the 11 U.S. studies; Table 5-17), and for Z in the range 1.5 to 3.0.

For RR_1 in the interval (8,11), the total lung cancer mortality from ETS ranges from about 2,600 to 3,500, a 14% change in either direction relative to the comparison total of 3,060. The extremes are much greater over the range of values considered for RR_2 (1.04 to 1.35). At the low end, where the excess relative risk from spousal ETS is only 4%, there is a 77% decrease in the total lung cancer mortality to 700. The percentage change is roughly equivalent in the opposite direction when the excess relative risk is at the maximum value 35%, for a total of 5,190. The total is also highly sensitive to the value of Z. A decrease of only 0.25 from the comparison value of $Z = 1.75$ increases the total by 36% to 4,160. A 36% decrease in ETS-attributable mortality occurs at $Z = 2.5$, leaving a corresponding estimate of 1,950. At $Z = 3.0$, the total drops further to 1,680, a 45% decrease.

Varying more than one parameter value simultaneously may have a compounding or canceling effect on the total lung cancer mortality due to ETS. For example, at the following

Table 6-6. Effect of single parameter changes on lung cancer mortality due to ETS in never-smokers and former smokers who have quit 5+ years

Parameter change		LCM due to ETS: Background[1]	Spousal[2]	Total	Percentage of change[3]
None[4]		**2,210**	**850**	**3,060**	**0**
Z =	1.50	3,310	850	4,160	+36
	1.75	**2,210**	**850**	**3,060**	**0**
	2.00	1,660	850	2,510	-18
	2.25	1,320	850	2,170	-29
	2.50	1,100	850	1,950	-36
	2.75	950	850	1,800	-41
	3.00	830	850	1,680	-45
RR_2 =	1.04	510	190	700	-77
	1.05	630	240	870	-72
	1.10	1,220	470	1,690	-45
	1.15	1,780	690	2,470	-19
	1.19	**2,210**	**850**	**3,060**	**0**
	1.20	2,310	890	3,200	+5
	1.25	2,820	1,080	3,900	+27
	1.30	3,290	1,270	4,560	+49
	1.35	3,750	1,440	5,190	+70
RR_1 =	8.00	2,510	970	3,480	+14
	8.50	2,380	920	3,300	+8
	9.00	2,260	870	3,130	+3
	9.26	**2,210**	**850**	**3,060**	**0**
	9.50	2,160	830	2,990	-2
	10.00	2,060	800	2,860	-7
	10.50	2,020	780	2,800	-9
	11.00	1,890	730	2,620	-14

[1]69,100,000 at risk.
[2]35,400,000 at risk.
[3]Percentage of change from total shown in boldface (the outcome from Tables 6-2 and 6-3, using the 11 U.S. studies).
[4]Z = 1.75, RR_2 = 1.19, RR_1 = 9.26.

whatever is used for "dose" in the dose-response curve, and that the risk calculated in this way applies equally to active and passive smokers with equivalent cotinine measures. The effect of differences in physico-chemical properties of mainstream smoke and sidestream smoke (the principal component of ETS), in lung dosimetry between active and passive smoking, and in exposure patterns (related to concentration and duration of exposure) are not fully understood, but the current state of knowledge casts doubts on the validity of these assumptions.

The remaining approach to population risk extrapolates to the general population from the epidemiologic evidence of increased relative risk of lung cancer in never-smoking women married to smokers. To extrapolate exposure and consequent risk to other sources of ETS exposure, cotinine levels of never-smokers exposed to spousal ETS are compared with those of never-smokers exposed only to other sources of ETS (background), and it is assumed that excess risks of lung cancer from ETS exposures, using cotinine levels as a surrogate measure, are proportional to current ETS exposure levels. (Here, cotinine levels are used to gauge relative levels of *ETS* exposure, not to extrapolate between active and passive smoking as in the "cigarette-equivalents" approach.) The use of current cotinine data to estimate ETS exposure in nonsmokers seems reasonable because cotinine levels correlate quite well with questionnaire response on ETS exposure. However, the total estimate of population risk is sensitive to uncertainty in making these assumptions and variability in the use of cotinine measures.

This report uses the modeling approach based on direct ETS epidemiologic evidence because the assumptions are fewer and more valid than for the "cigarette-equivalents" approach, and the abundance of human data from actual environmental exposures makes this preferred approach feasible. The total number of lung cancer deaths in U.S. females from all causes is partitioned into components attributable to non-tobacco-smoke-related causes (background causes unrelated to active or passive smoking), background ETS (also called nonspousal ETS), spousal ETS, and ever-smoking. Two sets of calculations are made for the U.S. female population age 35 and over in 1985 based on parameter values from national statistics and estimates from the epidemiologic studies on ETS and lung cancer. They differ in the values assumed for two parameters in the formulae for attributable risk: RR_2, the relative risk of lung cancer for never-smokers exposed to spousal smoke, and Z, the ratio of cotinine concentrations in never-smokers exposed to spousal ETS to those exposed to background ETS only. The first analysis uses the pooled estimate of RR_2 from the 11 U.S. studies from Chapter 5, and a subjective value of Z based on the outcomes of independent U.S. cotinine studies ($RR_2 = 1.19$ and $Z = 1.75$). The second analysis uses the estimates of RR_2 and Z from the large, high-quality Fontham et al. study

values of RR_2, the range of percentage changes from the total of 3,060 ETS-attributable lung cancer deaths for values of Z in the interval 1.50 to 3.0 are shown in parentheses: $RR_2 = 1.04$ (-69%, -88%), $RR_2 = 1.15$ (+10%, -56%), $RR_2 = 1.25$ (+73%, -30%), and $RR_2 = 1.35$ (+131%, -7%). The total ETS-attributable LCD estimates range from 380 (at $RR_2 = 1.04$, $Z = 3.0$) to 7,060 (at $RR_2 = 1.35$, $Z = 1.5$). Without considering the additional variability that other parameters might add, it is apparent that the estimated lung cancer mortality from ETS is very sensitive to the parameters RR_2 and Z and that the uncertainty in these parameters alone leaves a fairly wide range of possibilities for the true population risk.

While various extreme values of these parameters can lead to the large range of estimates noted, the extremities of this range are less likely possibilities for the true population risk because the parameters RR_2 and Z are not actually independent and would be expected to co-vary in the same direction, not in the opposite direction as expressed by the extreme values. For example, if the contributions of background to total ETS exposure decrease, Z would increase, and the observable relative risk from spousal exposure, RR_2, would be expected to increase as well. In addition, most of the evidence presented in this report suggests that a narrower range of both RR_2 and Z are appropriate. Thus, while substantially higher or lower values are conceivable, this report concludes that the estimate of approximately 3,000 ETS-attributable LCDs based on the 11 U.S. studies is a reasonable one. Furthermore, this estimate is well corroborated by the estimates of 2,700 and 3,600 calculated by analyzing the FONT data alone, the only study dataset from which estimates of both RR_2 and Z are obtainable.

6.4. SUMMARY AND CONCLUSIONS ON POPULATION RISK

Having concluded in the previous chapter that ETS is causally associated with lung cancer in humans and belongs in EPA Group A of known human carcinogens, this chapter assesses the magnitude of that health impact in the U.S. population. The ubiquity of ETS in a typical individual's living environment results in the respiratory uptake of tobacco smoke to some degree in a very high percentage of the adult population, conservatively upwards of 75% based on the outcome of urinary cotinine/creatinine studies in nonsmokers. Compared with observations on active smokers, body cotinine levels in nonsmokers are low, on the order of a few percent, and there is considerable variability in interindividual metabolism of nicotine to cotinine. Some authors have used the relative cotinine levels in active and passive smokers to estimate the probability of lung cancer in nonsmokers by extrapolating downward on a dose-response curve for active smokers. This "cigarette-equivalents" approach requires several assumptions, e.g., that the dose-response curve used for active smokers is reasonably accurate and low-dose extrapolation of risk for active smokers is credible, that cotinine is proportional (and hence a substitute for)

(1991), the sole U.S. study that collected cotinine data for its study population (RR_2 = 1.28 with mean Z = 2.0 and with median Z = 2.6).

The estimated lung cancer mortality in never-smoking women from ETS (background and spousal ETS) is 1,500 in the first analysis and 1,760 (1,340) in the second analysis for Z = 2.0 (2.6). When estimates for never-smoking males and former smokers (5+ year quitters) of both sexes are added, the corresponding totals are 3,060 and 3,570 (2,670). All of these figures are based on calculations in which unknown parameter values are replaced with numerical estimates that are subject to uncertainty, and departures in either direction cannot be precluded as unrealistic possibilities for the correct population risks. Nonetheless, because of the large database utilized and the extensive analysis performed, there is a high degree of confidence in the estimates derived for female never-smokers. The figures for male never-smokers and former smokers of both sexes are subject to more uncertainty because more assumptions were necessary for extrapolation from the epidemiologic results. The estimates for male never-smokers, in particular, may be on the low side because males generally are exposed to higher levels of background ETS than females. In summary, our analyses support a total of approximately 3,000 as an estimate for the annual U.S. lung cancer deaths in nonsmokers attributable to ETS exposure.

A quantitative estimate of the variance associated with the 3,000 estimate is not possible without many assumptions, both about the model and the accuracy of the parameters used to derive the population estimates. As exhibited in Table 6-6, we believe the largest variability to be associated with RR_2 and Z. Based on the statistical variations, estimates as low as 400 and as high as 7,000 are possible. However, where specific assumptions were made, we believe that they are generally conservative, and we expect that the actual number may be greater than 3,000.

A feature of variability not addressed in the range presented above is the correlation between RR_2 and Z. The greater the correlation, the smaller will be the expected variance of RR_{02}, resulting in a narrower range of lung cancer estimates. Because only one lung cancer study, FONT, allows RR_2 and Z to be jointly estimated, no assessment of this correlation is possible. However, the two point estimates derived from the FONT data--2,700 and 3,600--provide additional reassurance in the 3,000 estimate.

In conclusion, despite some unavoidable uncertainties, we believe these estimates of ETS-attributable lung cancer mortality to be fairly reliable, if not conservatively low, especially with respect to the male nonsmoker component. First, the weight of evidence that ETS is a human lung carcinogen is very strong. Second, the estimates are based on a large amount of data from various studies of human exposures to actual environmental levels of ETS. They do not suffer from a need to extrapolate from an animal species to humans or from high to low exposures, as is nearly always the case in environmental quantitative health risk assessment. Thus, the confidence in

these estimates is judged to be medium to high. In summary, the evidence demonstrates that ETS has a very substantial and serious public health impact.